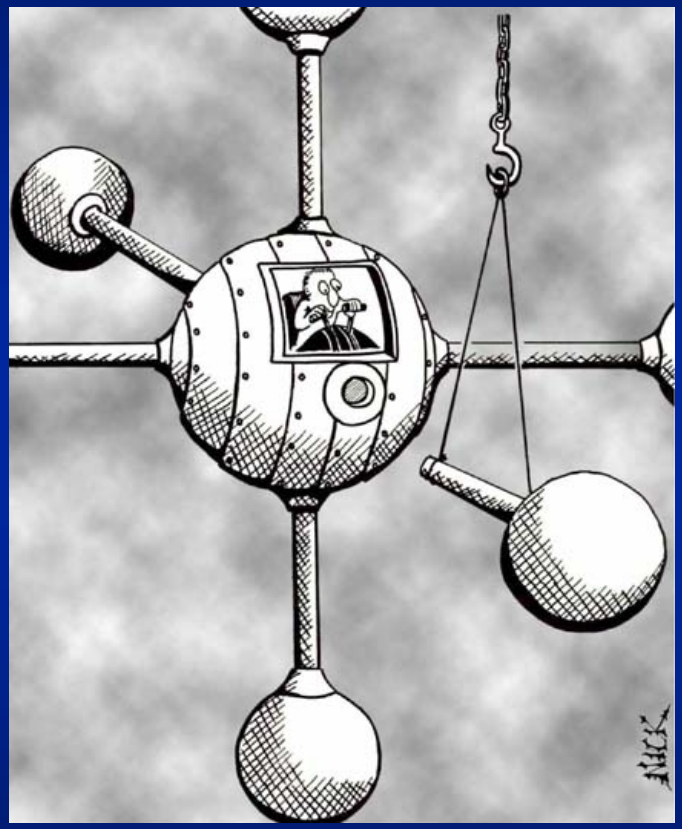
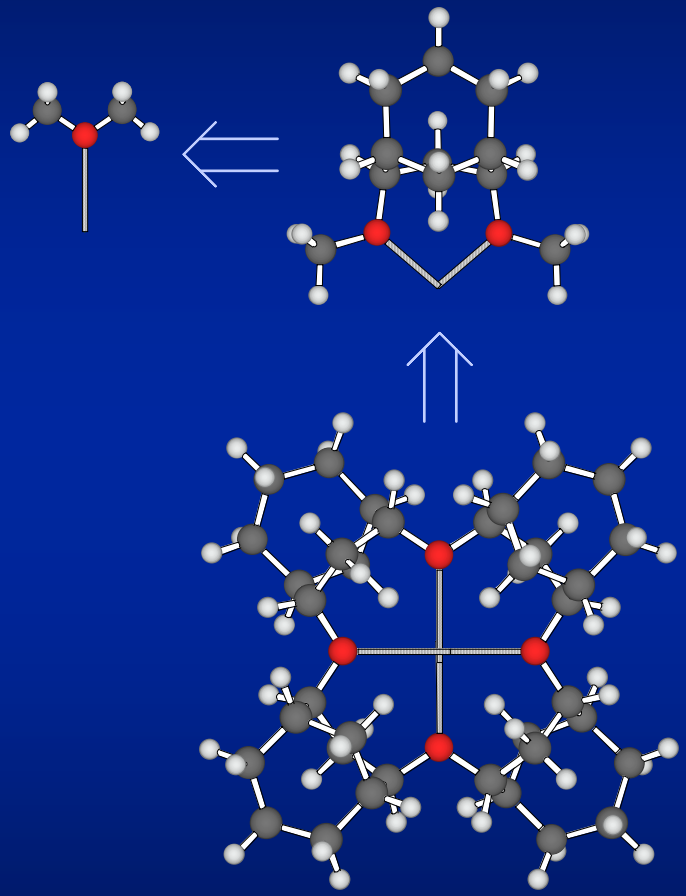
Computer-Aided Design of Ion Receptors





Benjamin P. Hay, April 17, 2006, Idaho National Laboratory

DOE Hanford Site

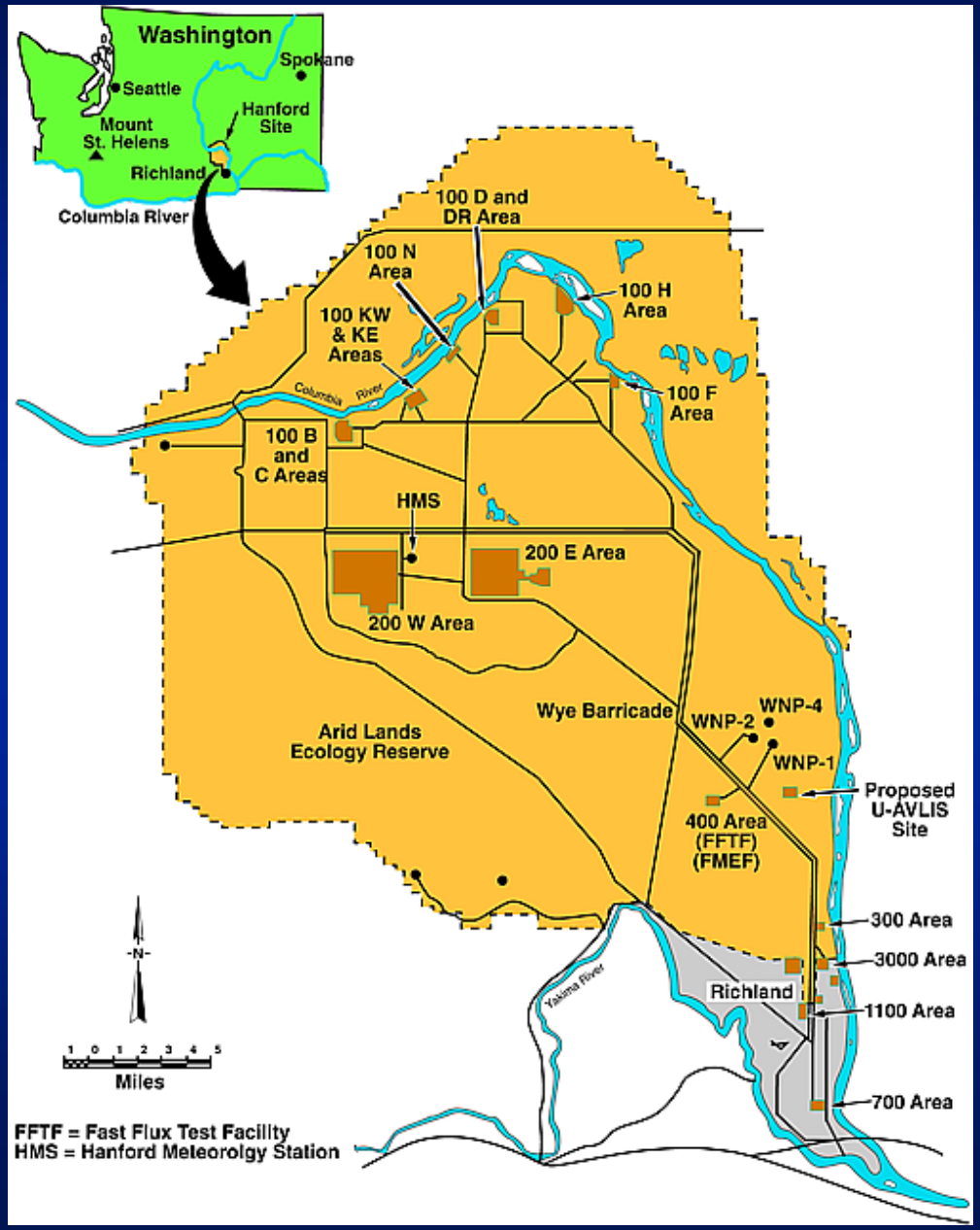
1942 - 1987 mission:

Plutonium production

1987 to date mission:

Clean-up

- decommission facilities
- decontamination
- stabilize nuclear waste
- environmental restoration



Motivation

50 years of weapons production:

- Uranium Mining, Milling, and Refinement
- Isotope Separation (Enrichment)
- Fuel and Target Fabrication
- Reactor Operations
- Chemical Separations
- Weapons Component Fabrication
- Weapons Operations
- Research, Development, and Testing

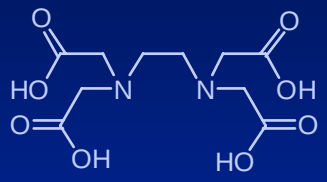
400,000 m^3 high-level nuclear waste
220,000 m^3 TRU waste
3.3 million m^3 low-level nuclear waste
1.4 billion m^3 environmental contamination

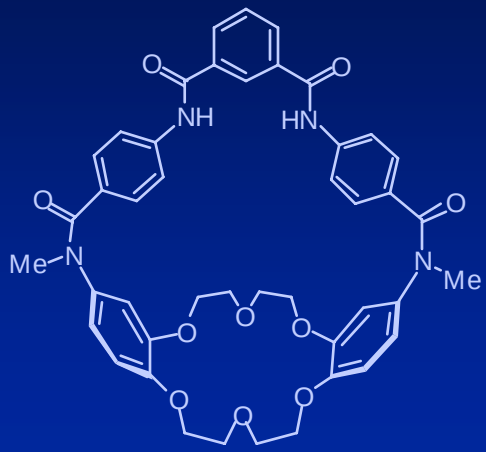
Bulk of radioactivity from metals:

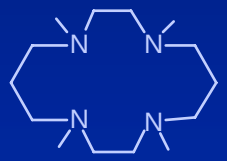
Co-60, Sr-90,
Y-90, Tc-99,
Sm-131, Cs-137,
Ba-137, Eu-152,
Eu-154, Eu-155,
Ra-226, Th-230,
U-233, U-235,
U-238, Pu-238,
Pu-239, Pu-240,
Pu-241, Am-241,
Cm-244

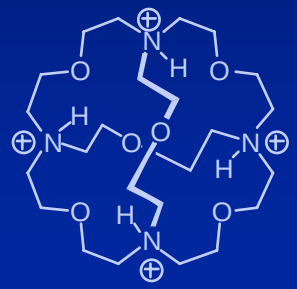
Data from “Linking Legacies”, DOE/EM-0319, January 1997

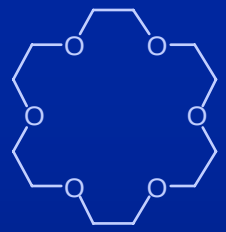
Ionophores play a key role in separations and analysis

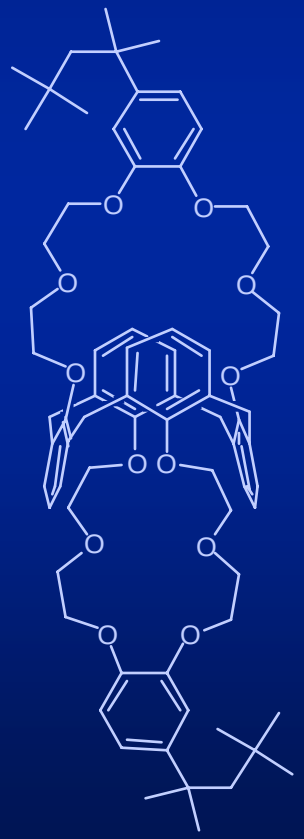


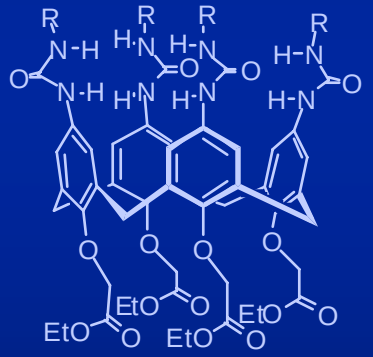


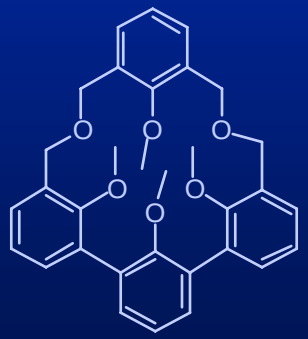


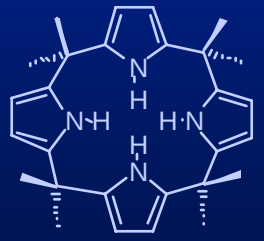


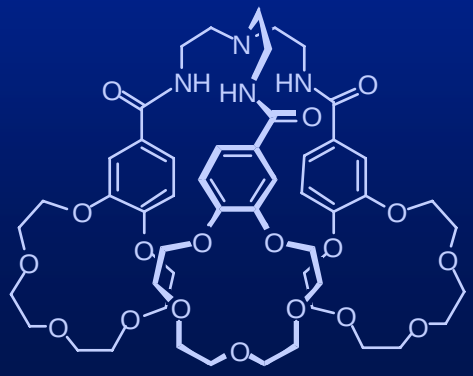




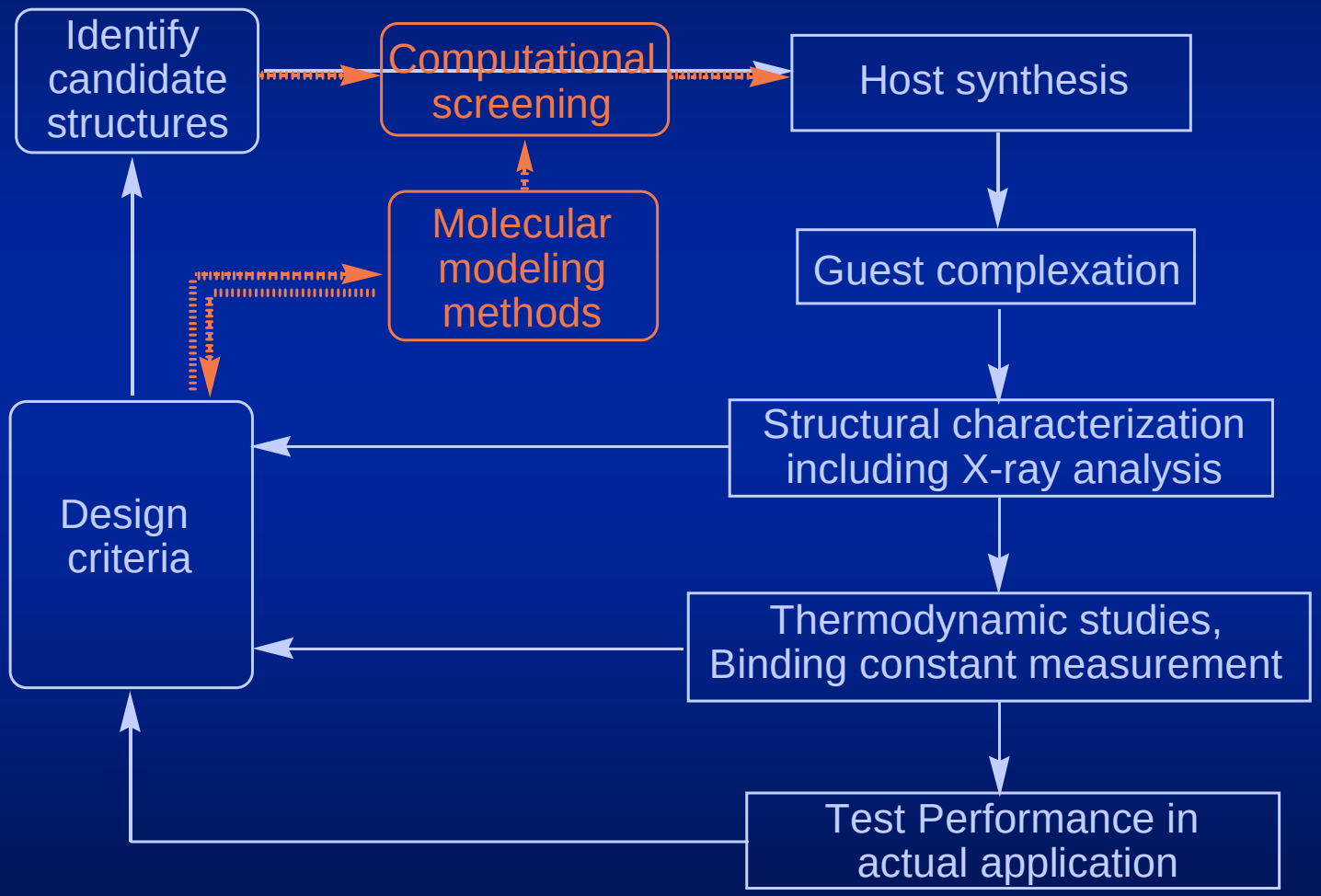






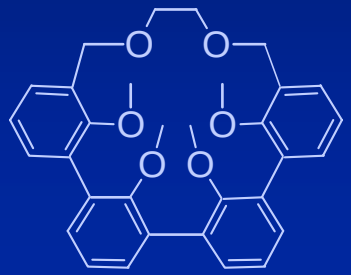


Computer-Aided **Host Design** ?

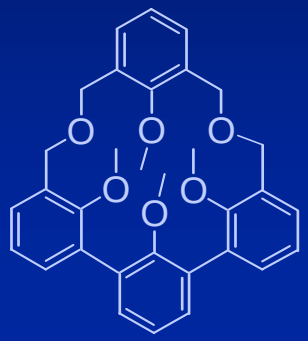


Architecture - scaffolds used to connect sets of binding sites

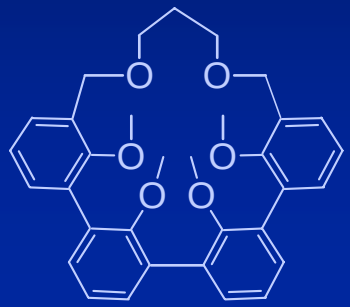
Structure can have a large effect on binding affinity:



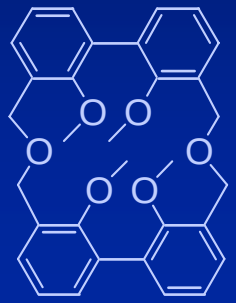
10^{10}



10^{6}



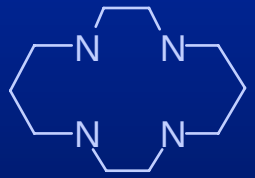
10^{5}



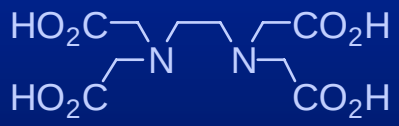
10^{3}

and significant impacts on selectivity:

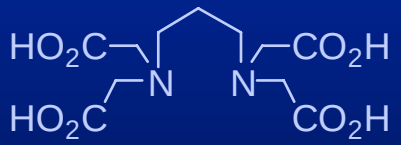
$Hg^{2+}/Cu^{2+} = 5$



$Cu^{2+}/Hg^{2+} = 10^{4}$

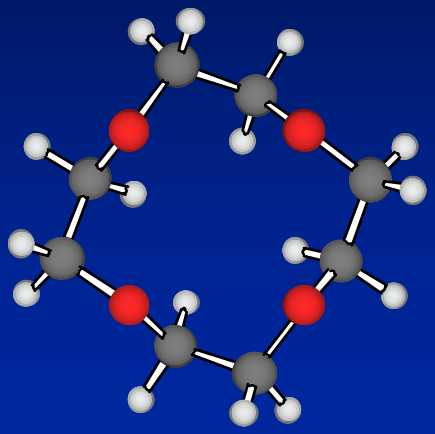


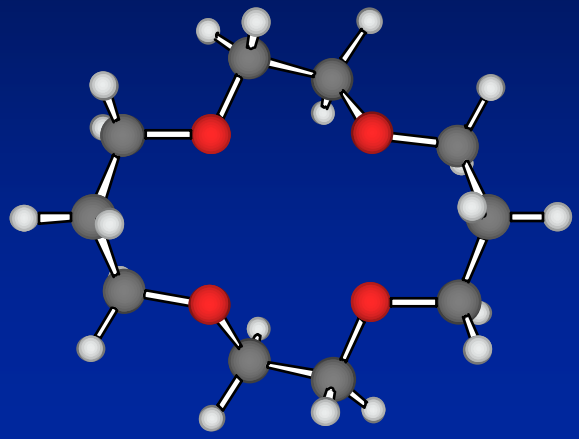
$Eu^{3+}/Al^{3+} = 13$

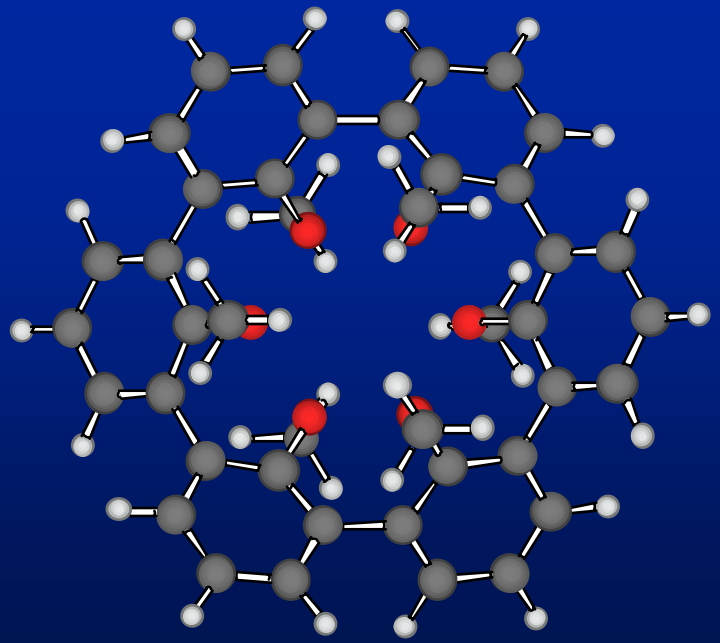


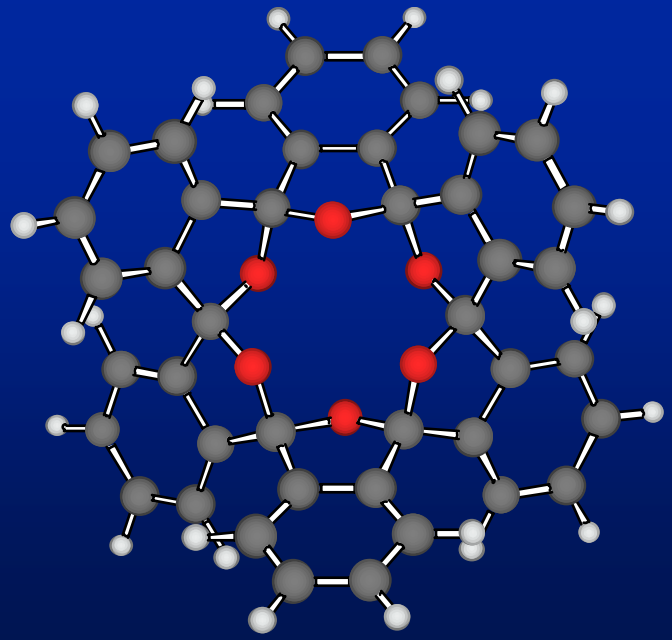
$Al^{3+}/Eu^{3+} = 500$

Structural effects are often difficult to predict

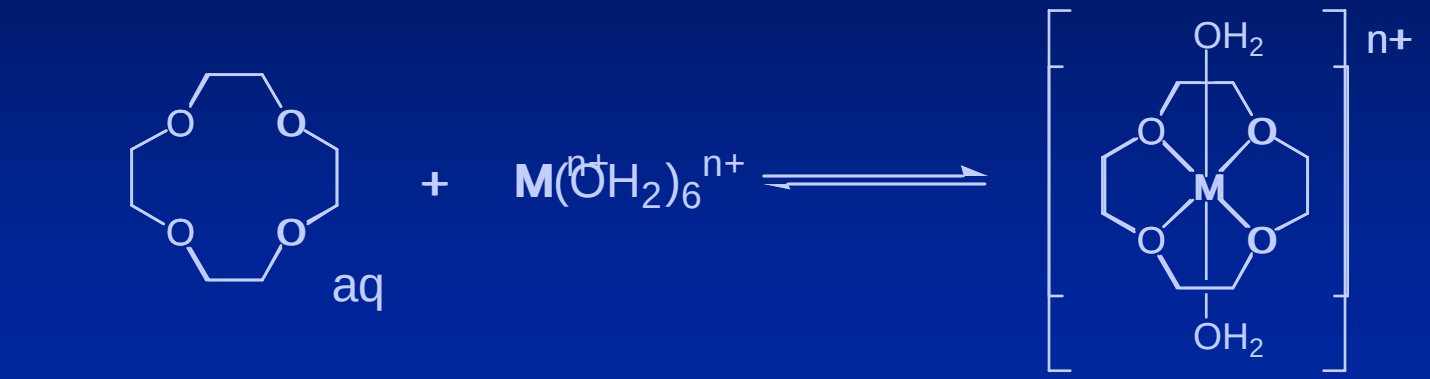


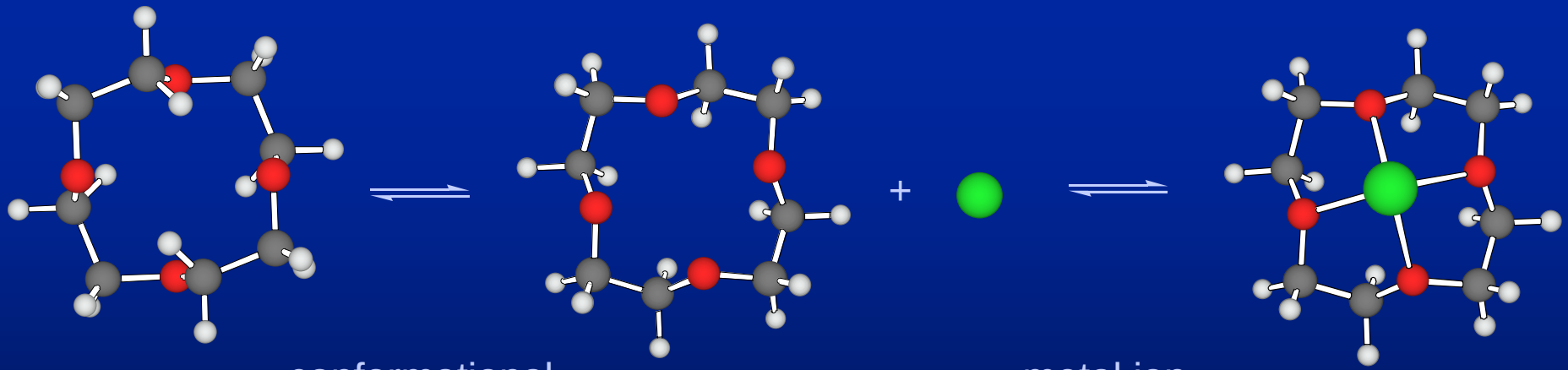






How do we approach this problem?





conformational reorganization

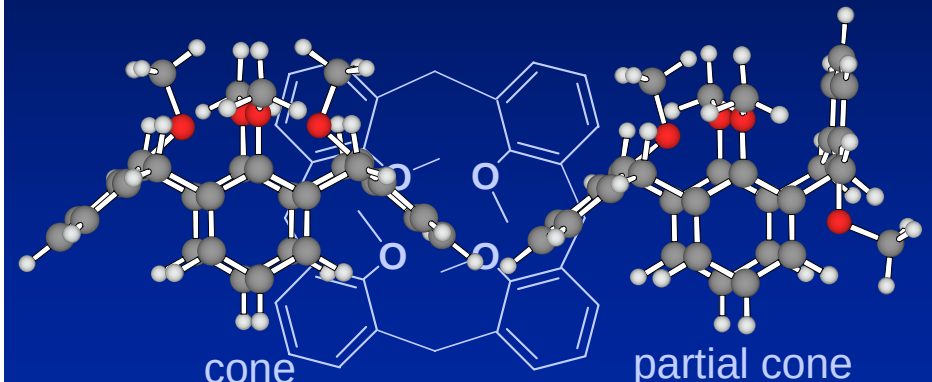
metal ion complexation

free form

binding form

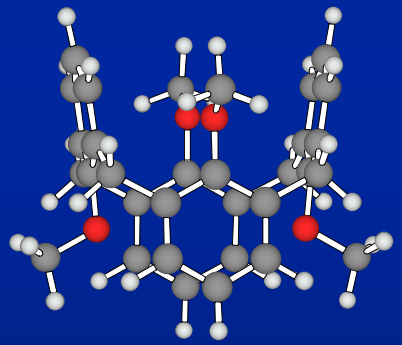
bound form

Electronic structure calculations

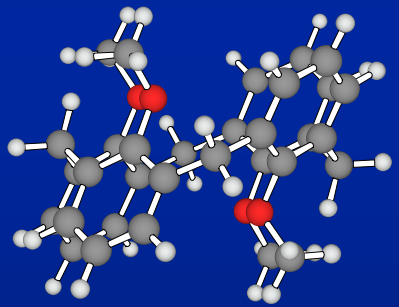


cone

partial cone



1,3 alternate

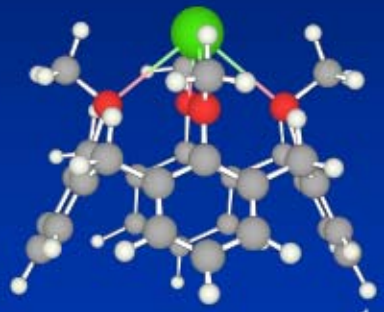


1,2 alternate

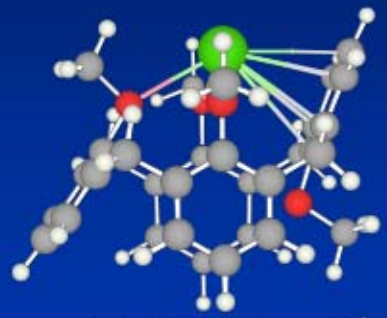
Electronic structure calculations

cone

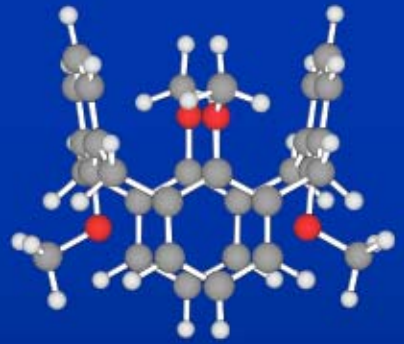
partial cone



-22.57 kcal mol^{-1}



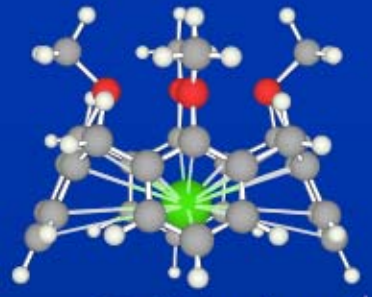
-31.10 kcal mol^{-1}



1,3 alternate

1,2 alternate

-33.98 kcal mol^{-1}



-35.14 kcal mol^{-1}

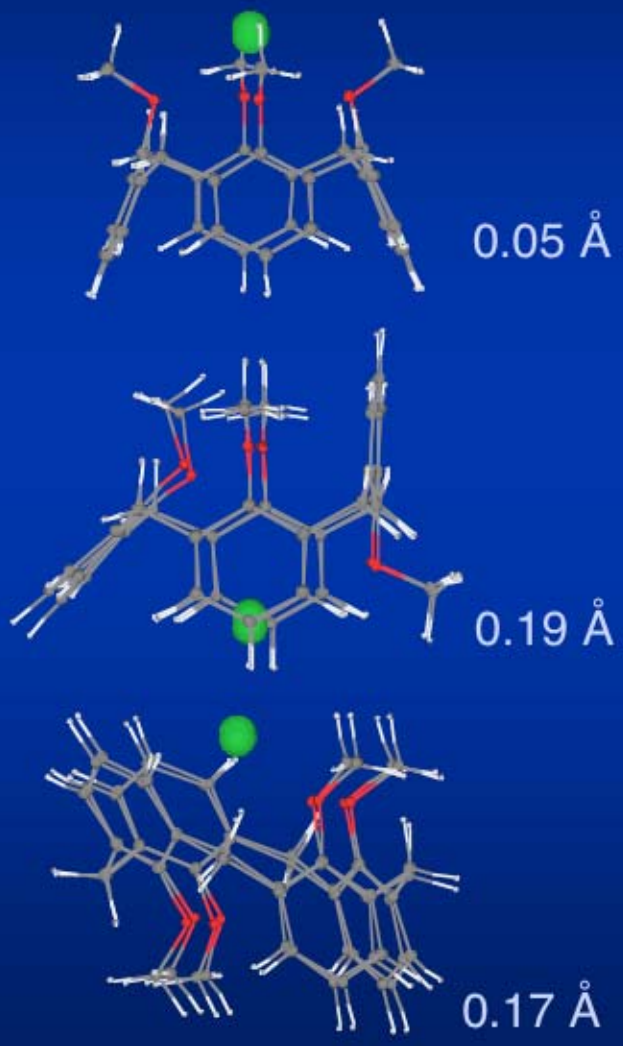
MP2/aug-cc-pVDZ//
BLYP/6-31+G*

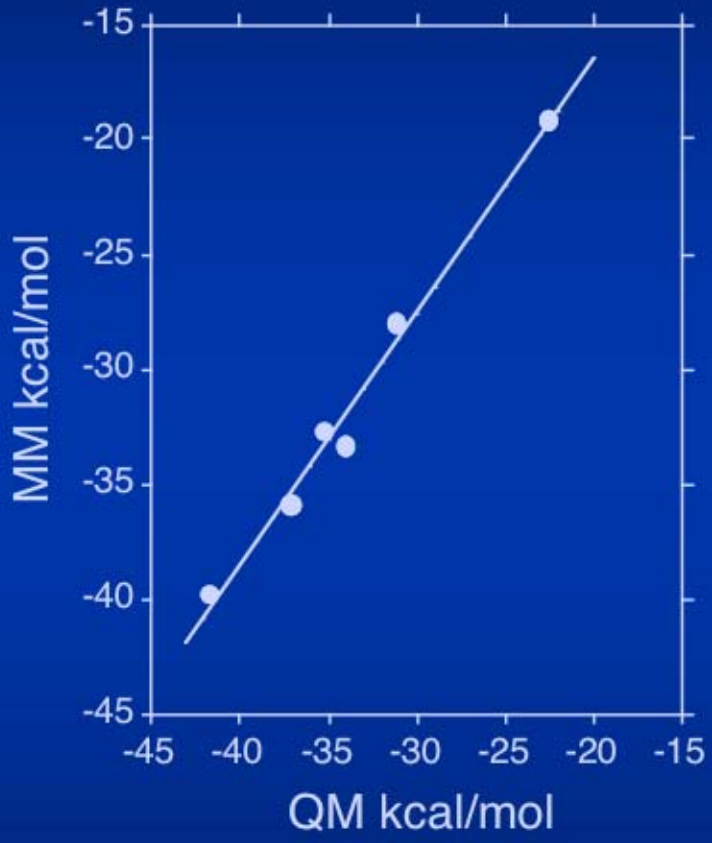
50,000 cpu/hr
(6 cpu/years for 10 structures)

-37.07 kcal mol^{-1}

-41.65 kcal mol^{-1}

Force field calculations are much, much quicker

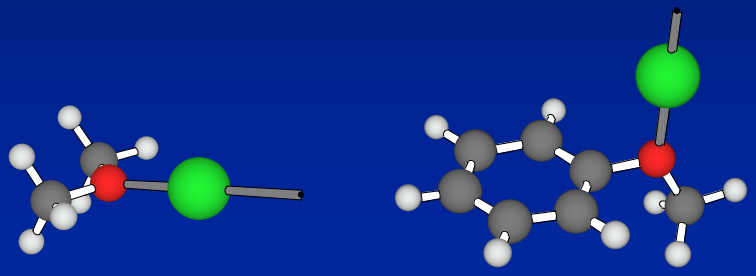




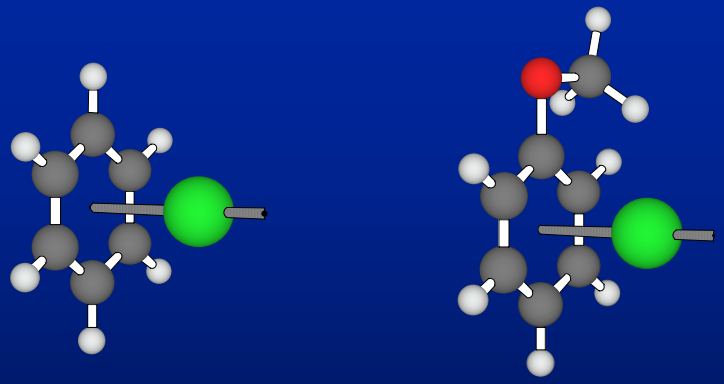
MM3 calculations take
5 seconds/structure on
a laptop computer

Downside - MM models require parameterization

High–level electronic structure calculations on simple analogs

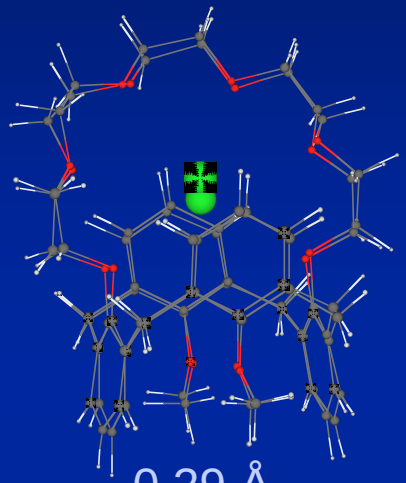


ether donors

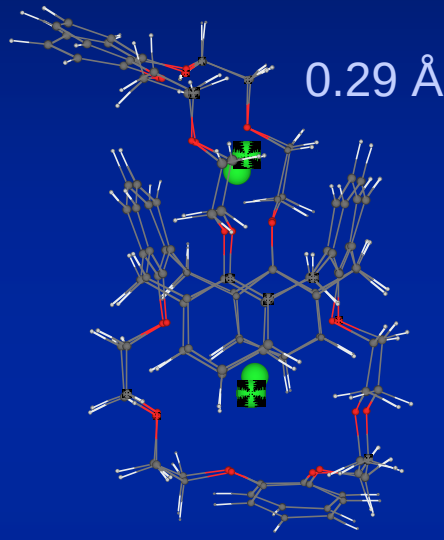


arene donors

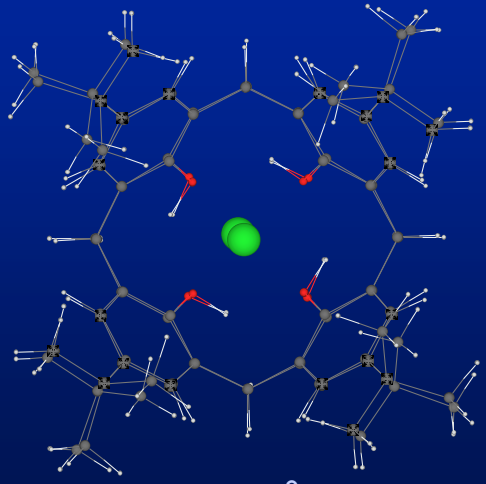
Crystal structure data



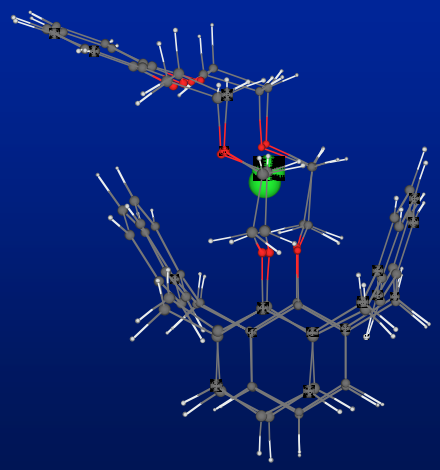
0.29 Å



0.29 Å

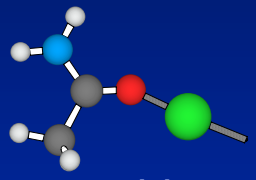


0.23 Å

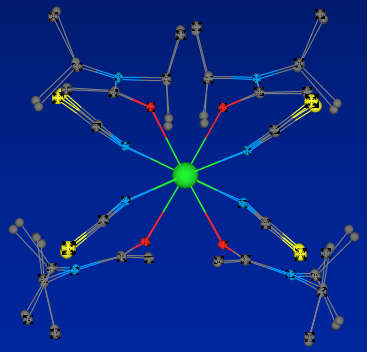


0.25 Å

Extending MM models to treat metal complexes

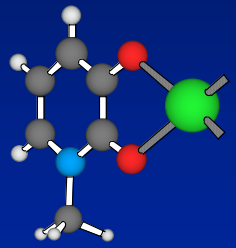


amide

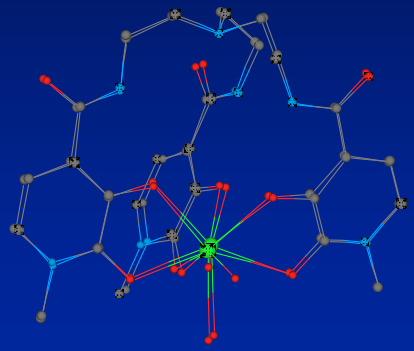


$[U(L)_4(SCN)_4]$

0.14 Å

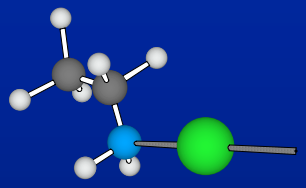


HOPO

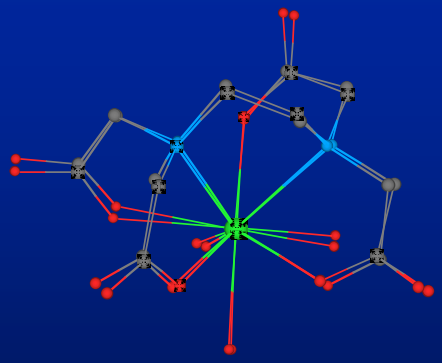


$[Gd(L)(OH_2)_2]$

0.19 Å

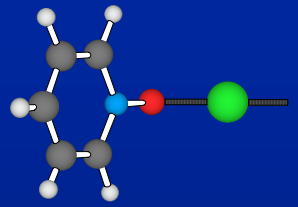


amine

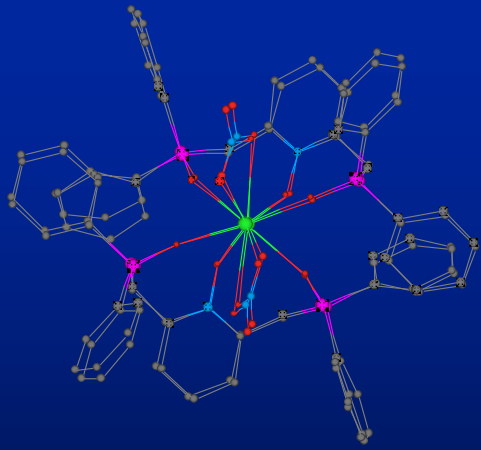


$[Nd(L)(OH_2)_3]^-$

0.17 Å

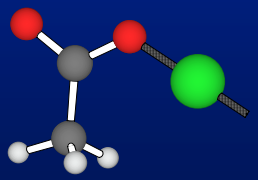


pyridine N-oxide

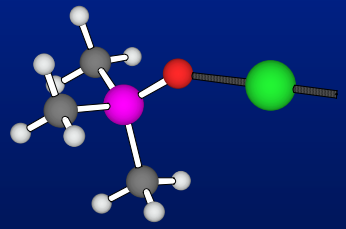


$[Pu(L)_2(NO_3)_2]^{2+}$

0.25 Å

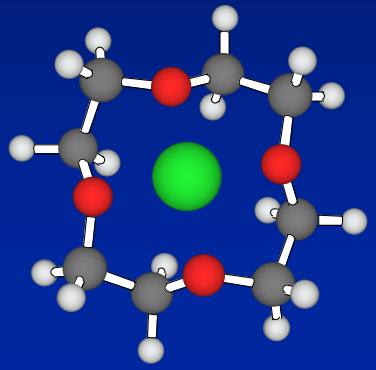


carboxylate

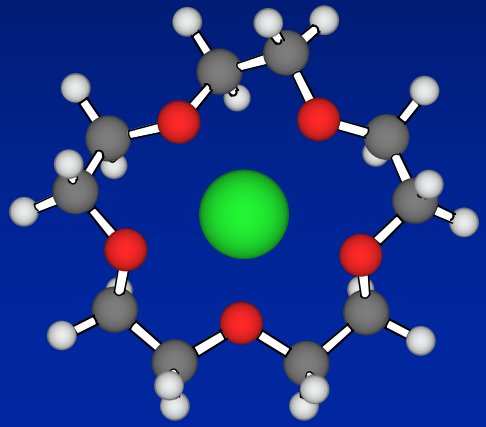


phosphine oxide

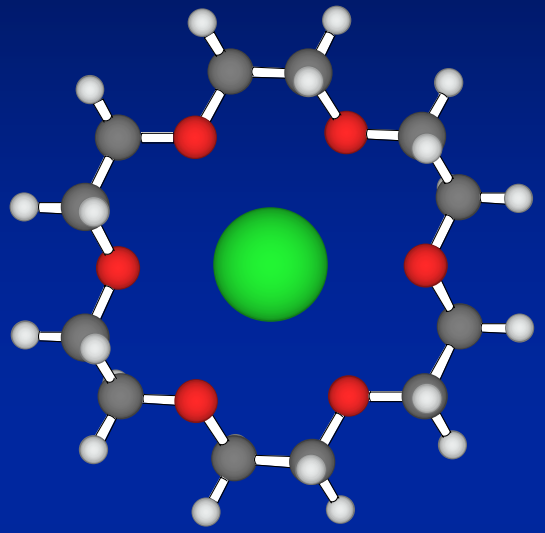
What can we learn by examining structures?



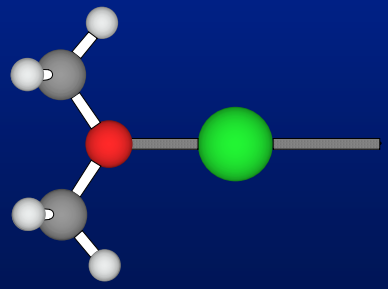
Li^+
12-crown-4

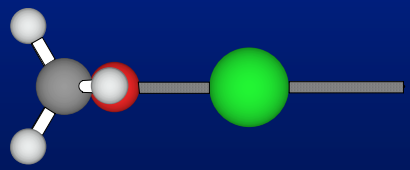


Na^+
15-crown-5

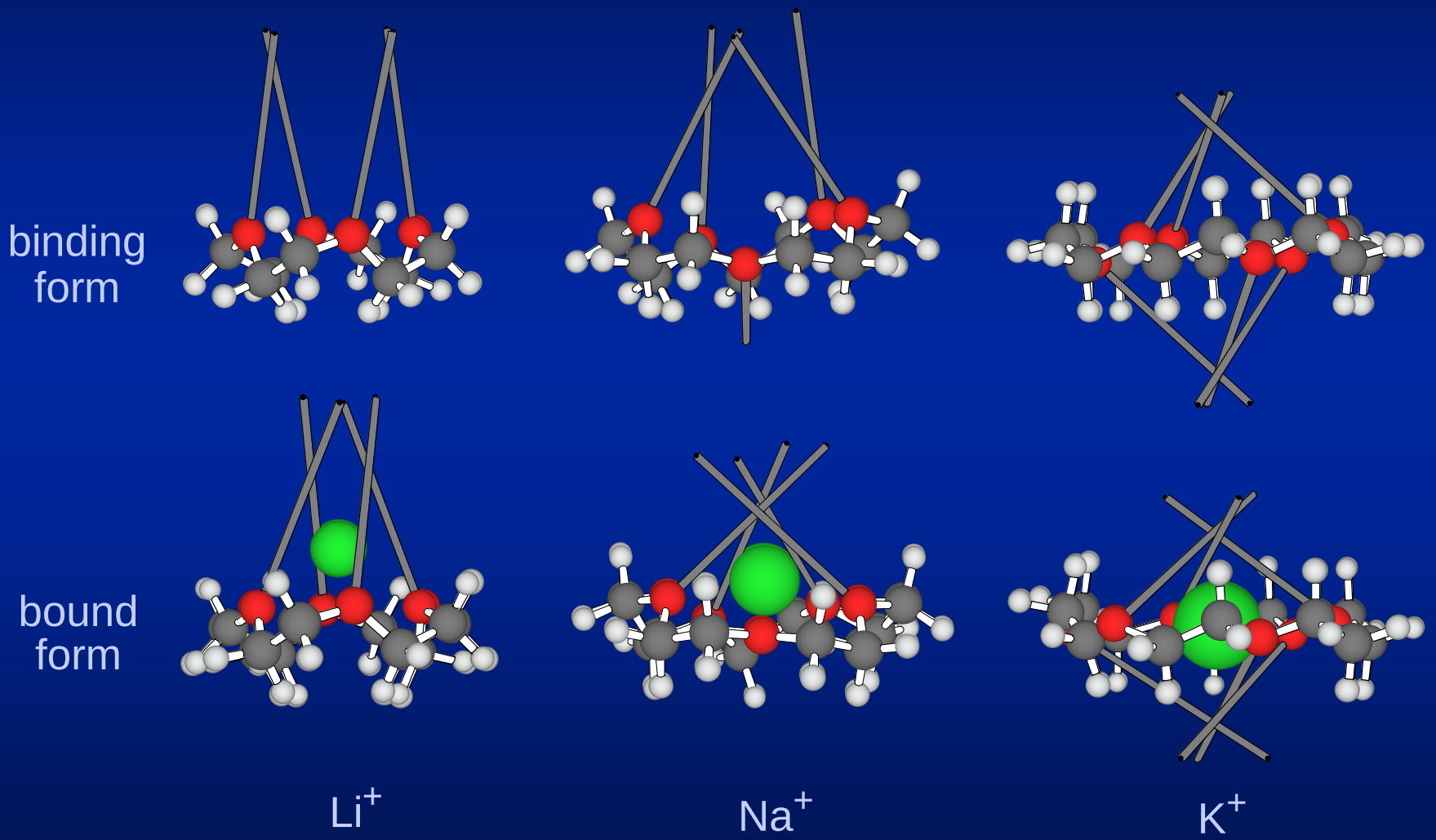


K^+
18-crown-6

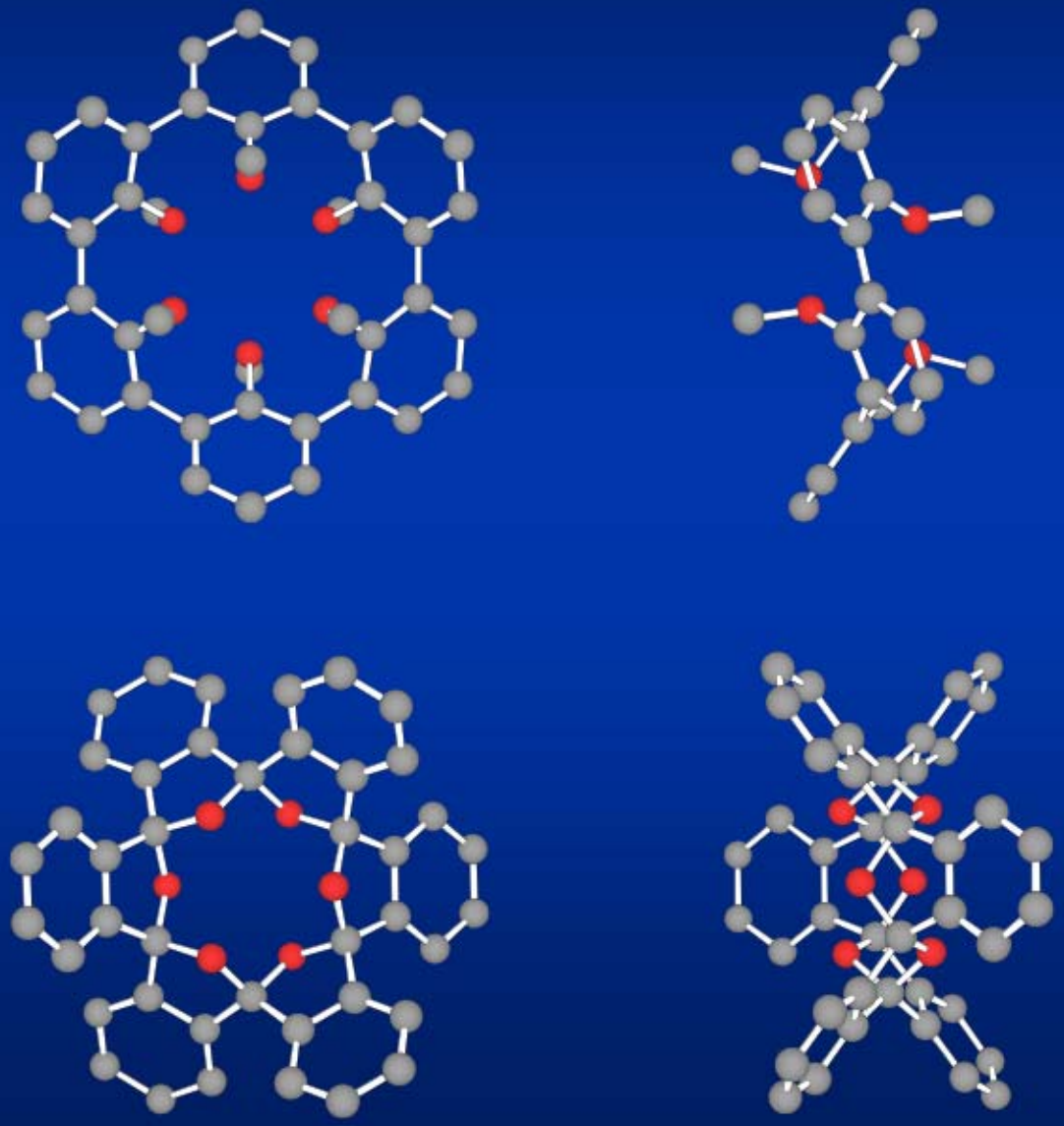




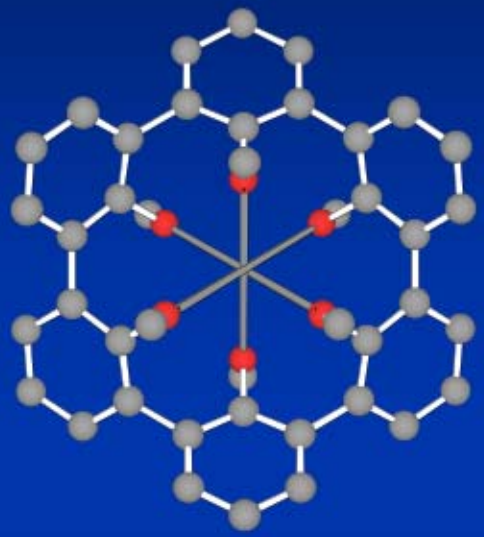
Binding site geometry in crowns favors large metals

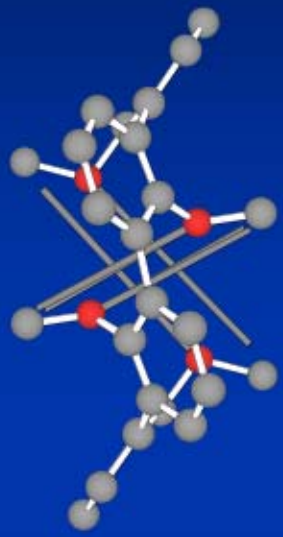


Size–match is not sufficient for complementarity

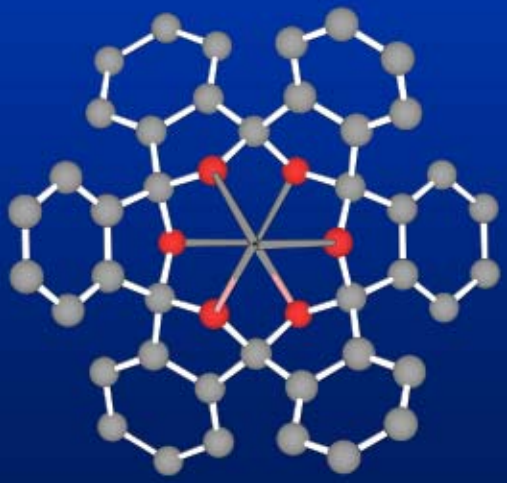


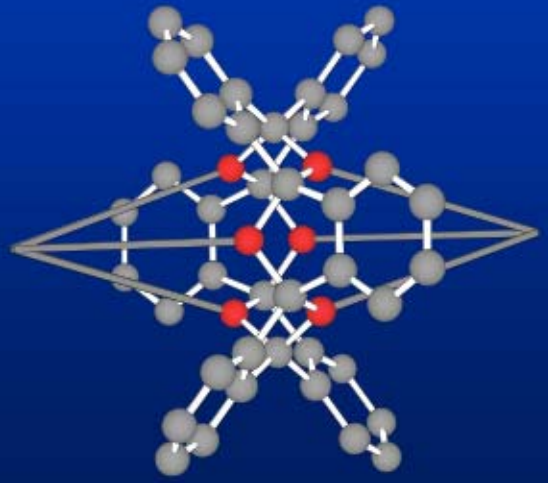
Size–match is not sufficient for complementarity





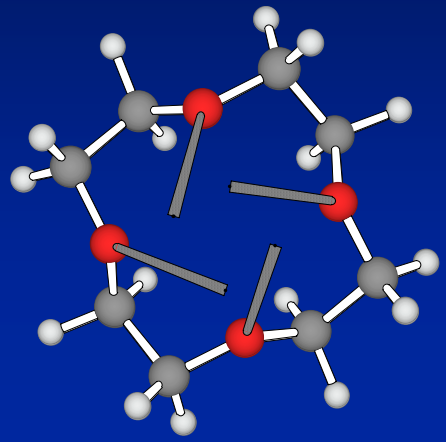
good donor orientation

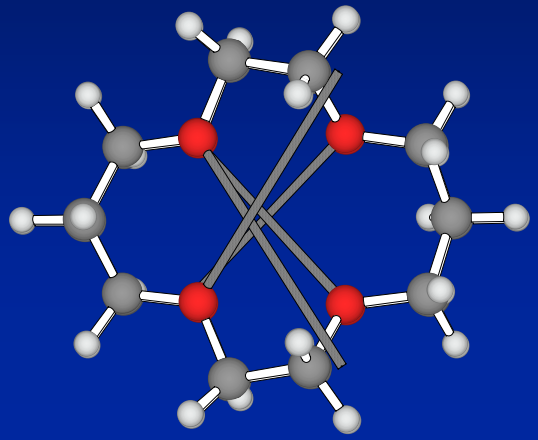


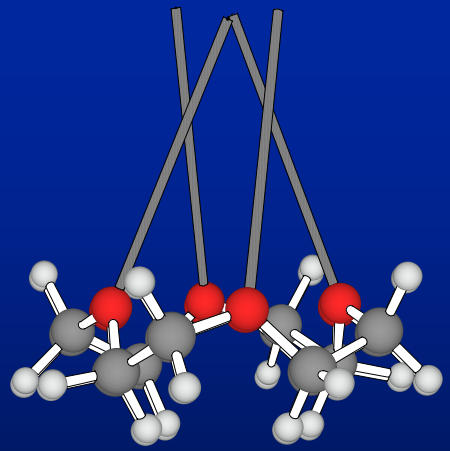


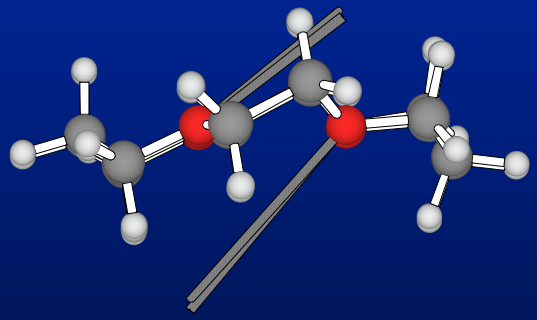
bad donor orientation

12-crown-4 versus 14-crown-4



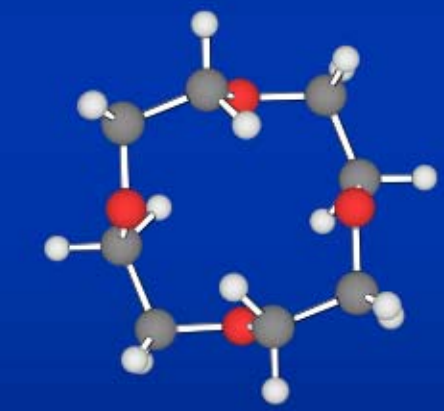






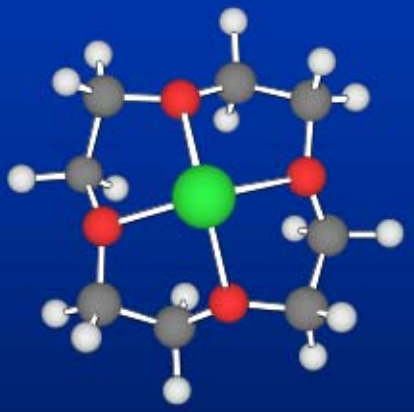
Host strain energy

Host strain energy



+

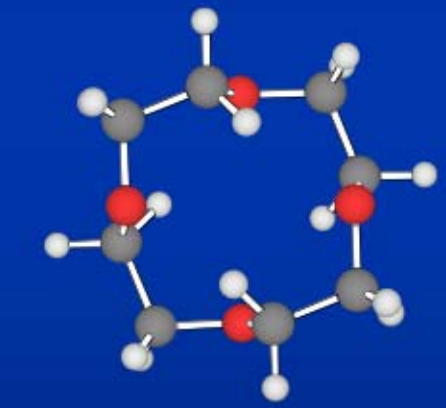
free



complex

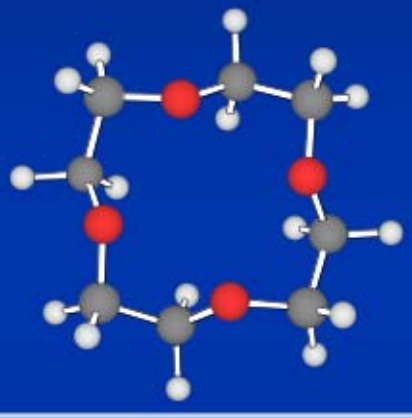
Host strain energy

$\Delta U_{tot} = \Delta U_1 + \Delta U_2$



free

ΔU_1



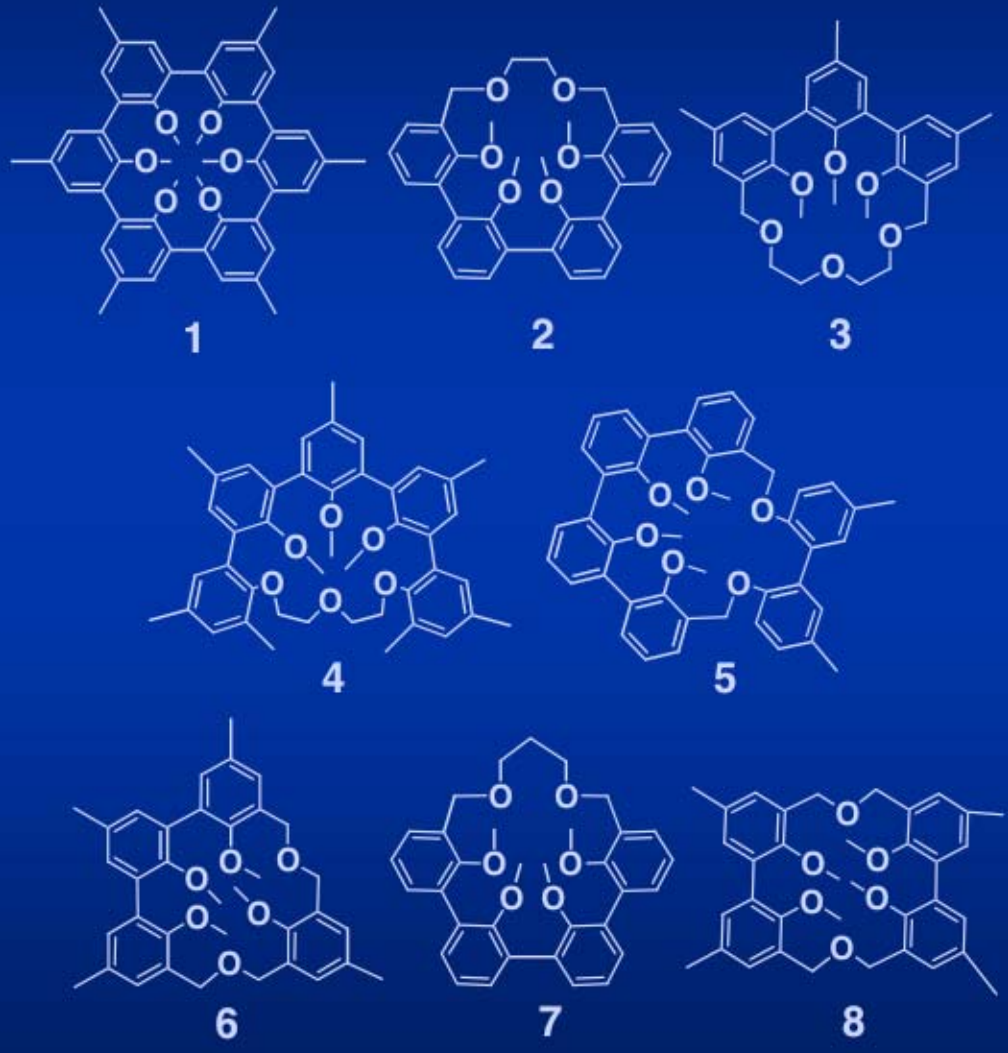
binding

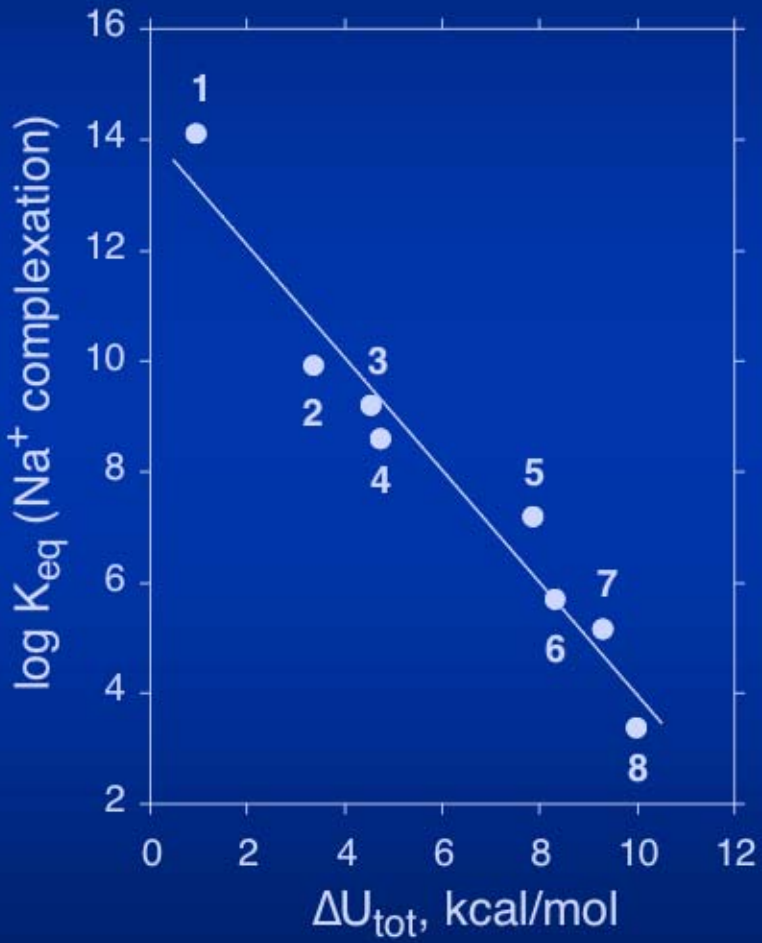
ΔU_2

bound

complex

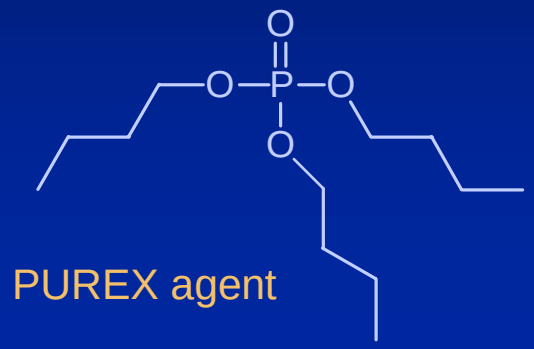
Binding affinity vs. host strain





Actinide sequestering agent design

Selective removal of Pu and U from spent fuel is done via solvent extraction:

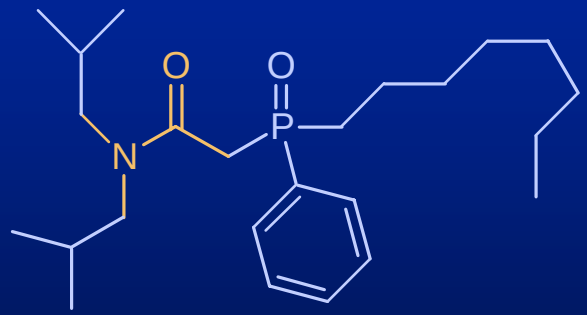


PUREX agent

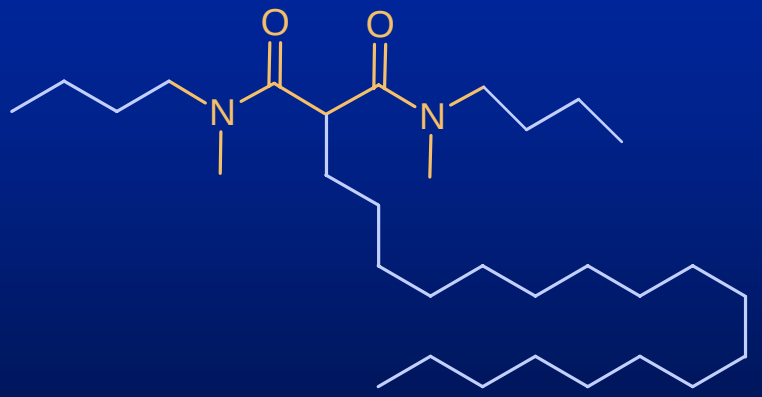
Used at Hanford from 1956 through 1987

Currently used for reprocessing power reactor fuel in France, UK, Japan, and Russia.

Agents that also remove Am(III) and Cm(III):

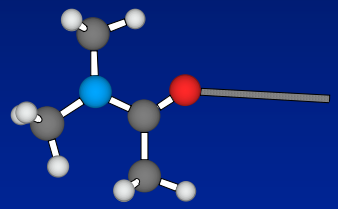


TRUEX agent (ANL/Eichrom)

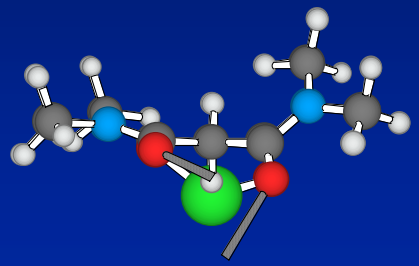


DIAMEX agent (Numatec)

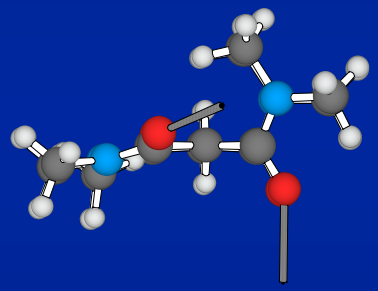
A closer look at the malonamide architecture



optimal orientation



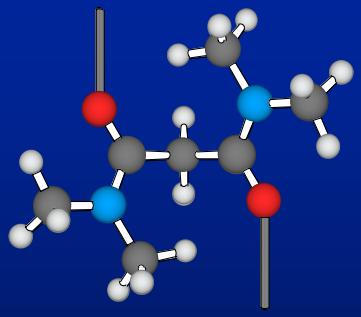
bound form



binding form

2.5 kcal/mol

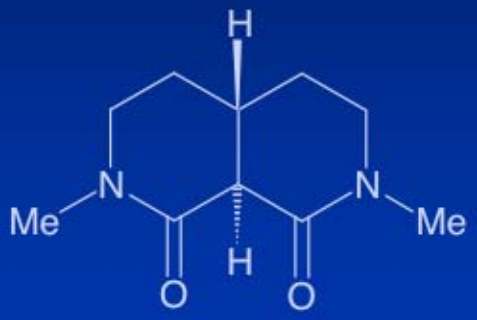
5.5 kcal/mol



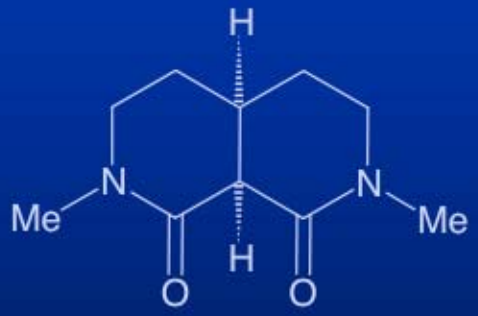
free form

3.0 kcal/mol

Improved architecture?

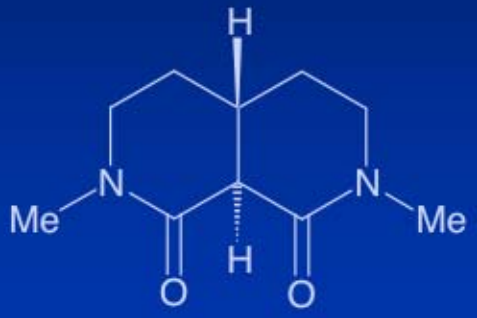


trans

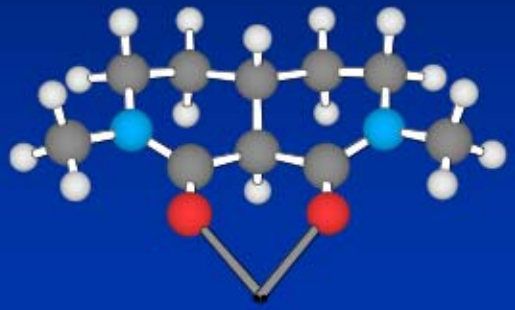


cis

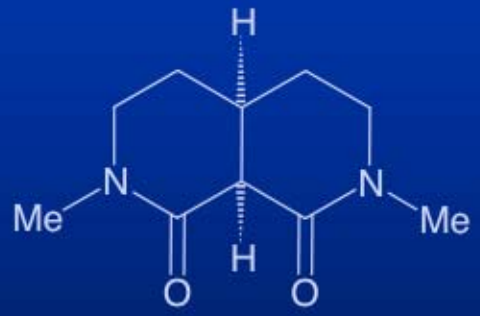
Improved architecture?



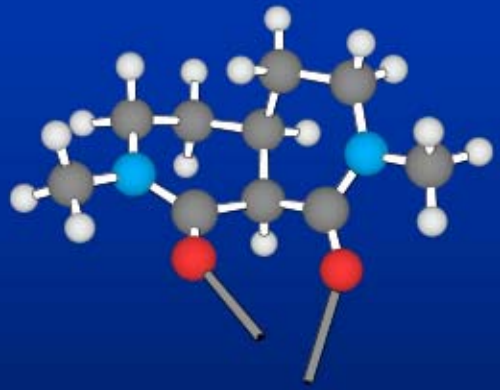
trans



ΔU_{tot} = 0.0 kcal/mol

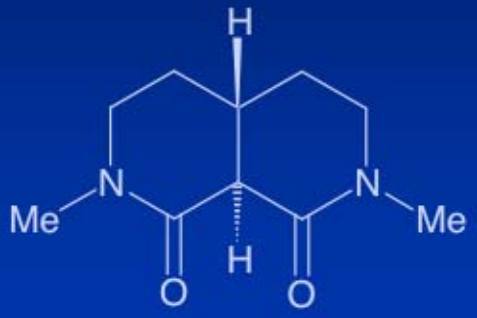


cis

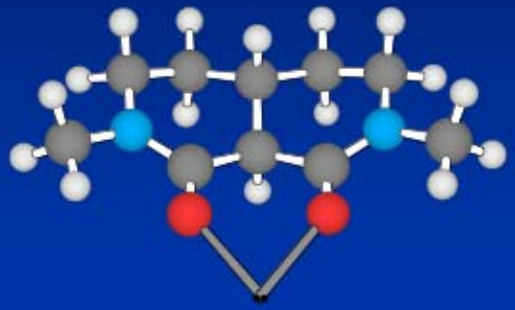


ΔU_{tot} = 0.1 kcal/mol

Improved architecture?

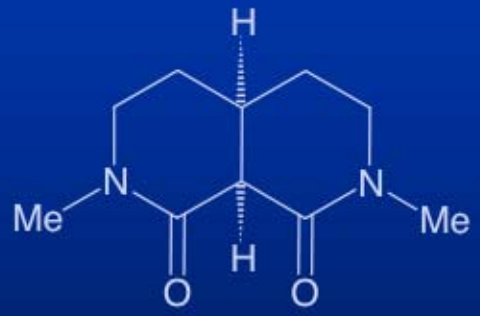


trans

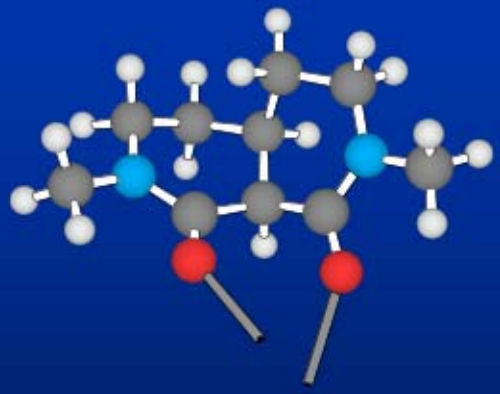


ΔU_{tot} = 0.0 kcal/mol

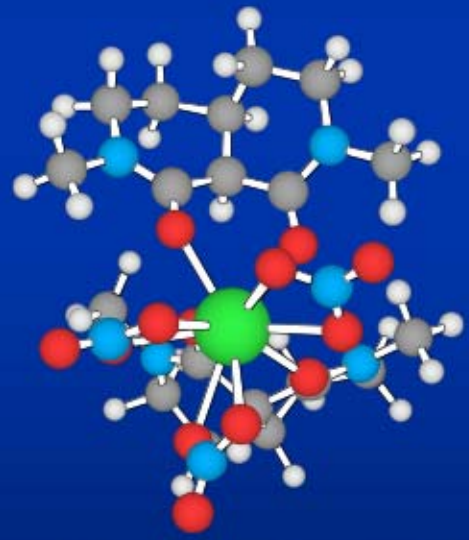
Synthesis yields only the *cis* form



cis

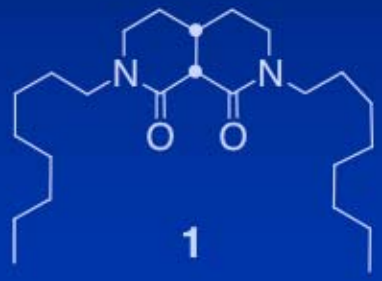


ΔU_{tot} = 0.1 kcal/mol

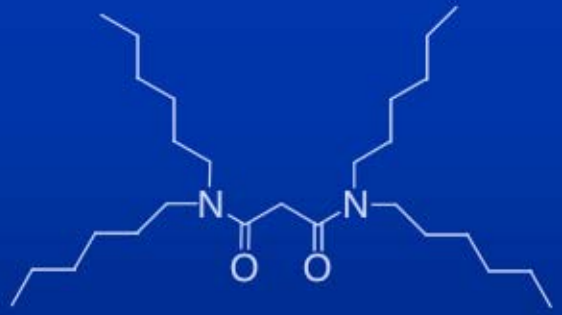


X-ray structure of $[Eu(L)_2(NO_3)_3]$

Proof in the pudding . . .

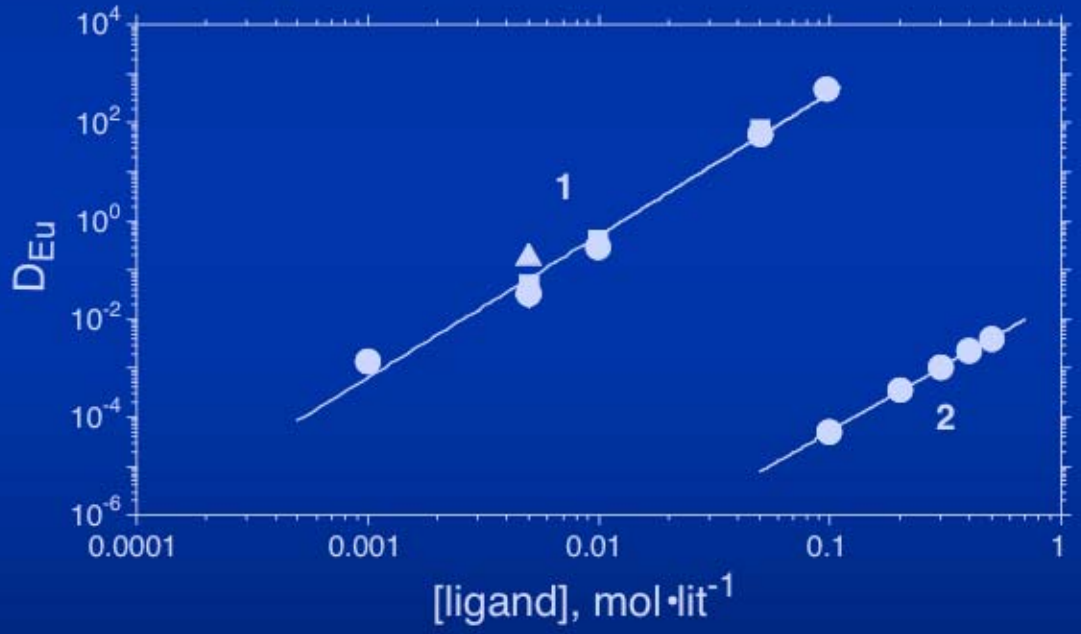


1

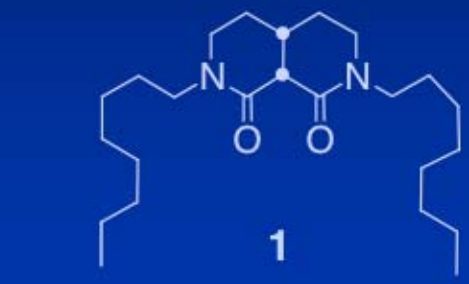


2

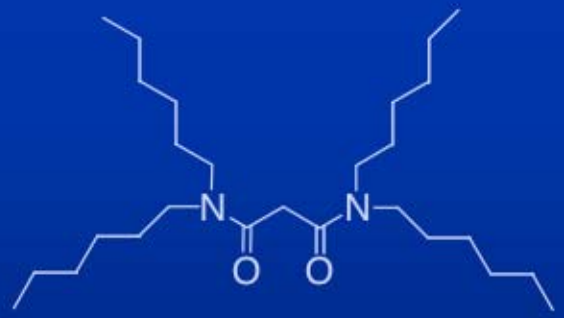
Extraction into t-butylbenzene from aqueous solution containing 1 M $NaNO_3$, 1.5 mM HNO_3, 0.1 mM $Eu(N0_3)_3$, and 1-μL of ^{155}Eu tracer solution.



Proof in the pudding . . .

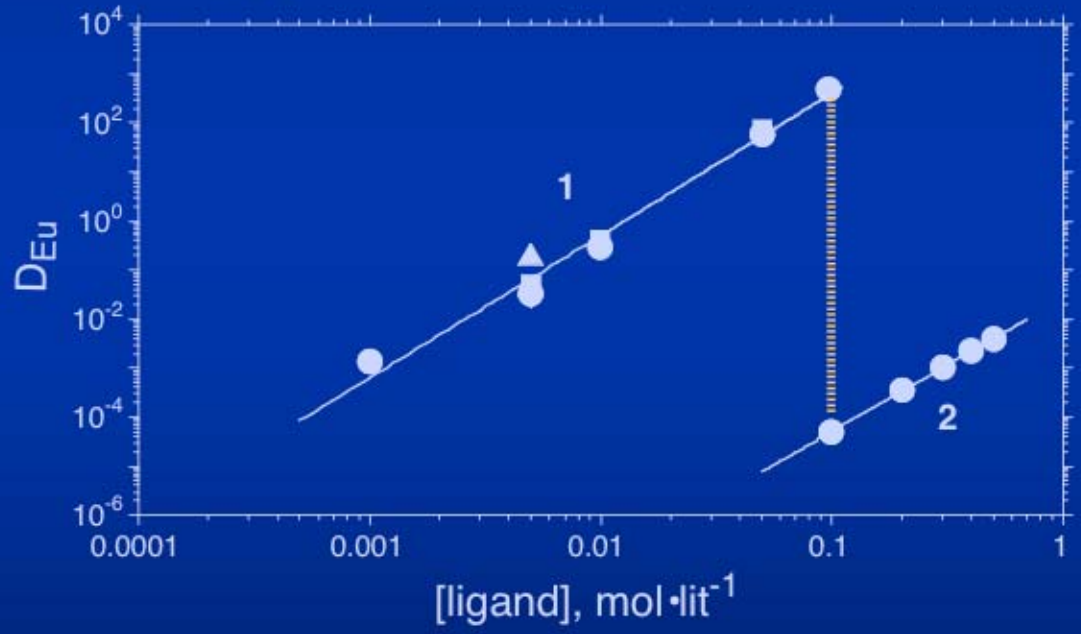


1



2

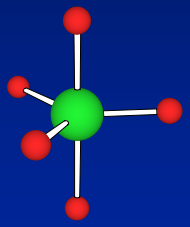
Extraction into t-butylbenzene from aqueous solution containing 1 M $NaNO_3$, 1.5 mM HNO_3, 0.1 mM $Eu(N0_3)_3$, and 1-μL of ^{155}Eu tracer solution.

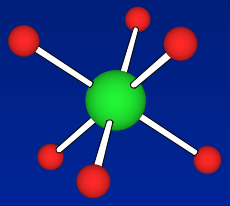


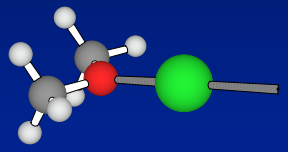
10 million times more effective

Lumetta, G. J.; Rapko, B. M.; Hay, B. P.; Gilbertson, R. D.; Weakly, T. J. R.; Hutchison, J. E. *J. Am. Chem. Soc.* **2002**, *124*, 5644.

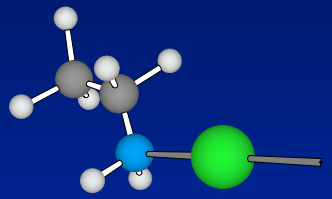
Structural design criteria



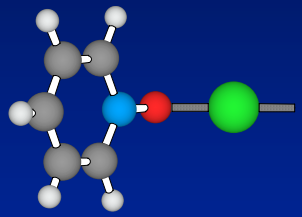




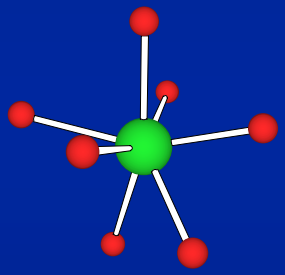
ether

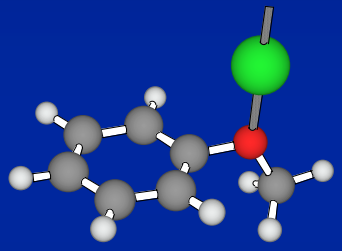


amine

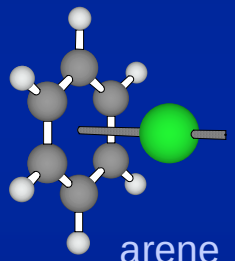


pyridine N-oxide

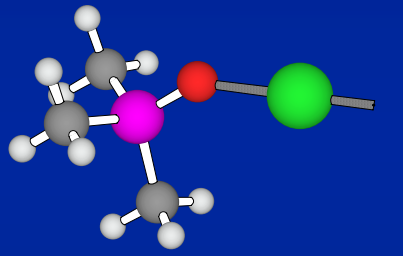




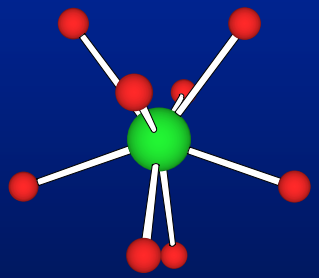
aryl ether

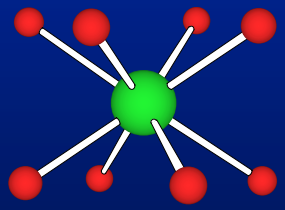


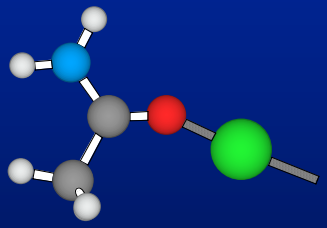
arene



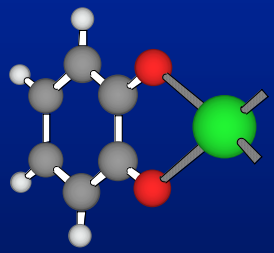
phosphine oxide



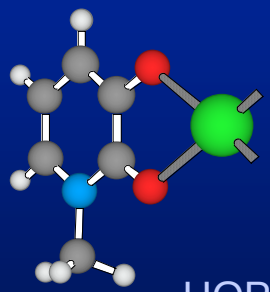




amide

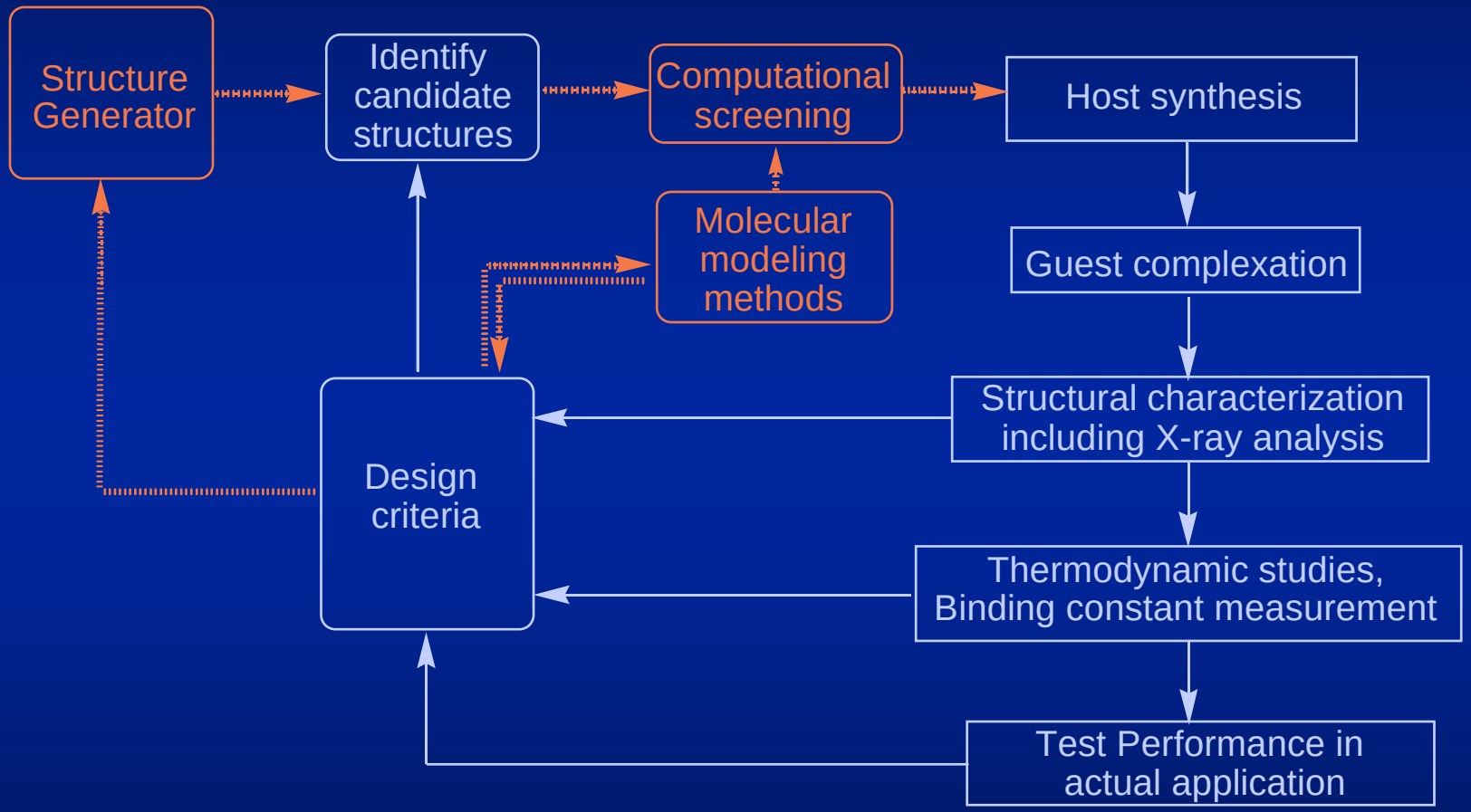


catecholate

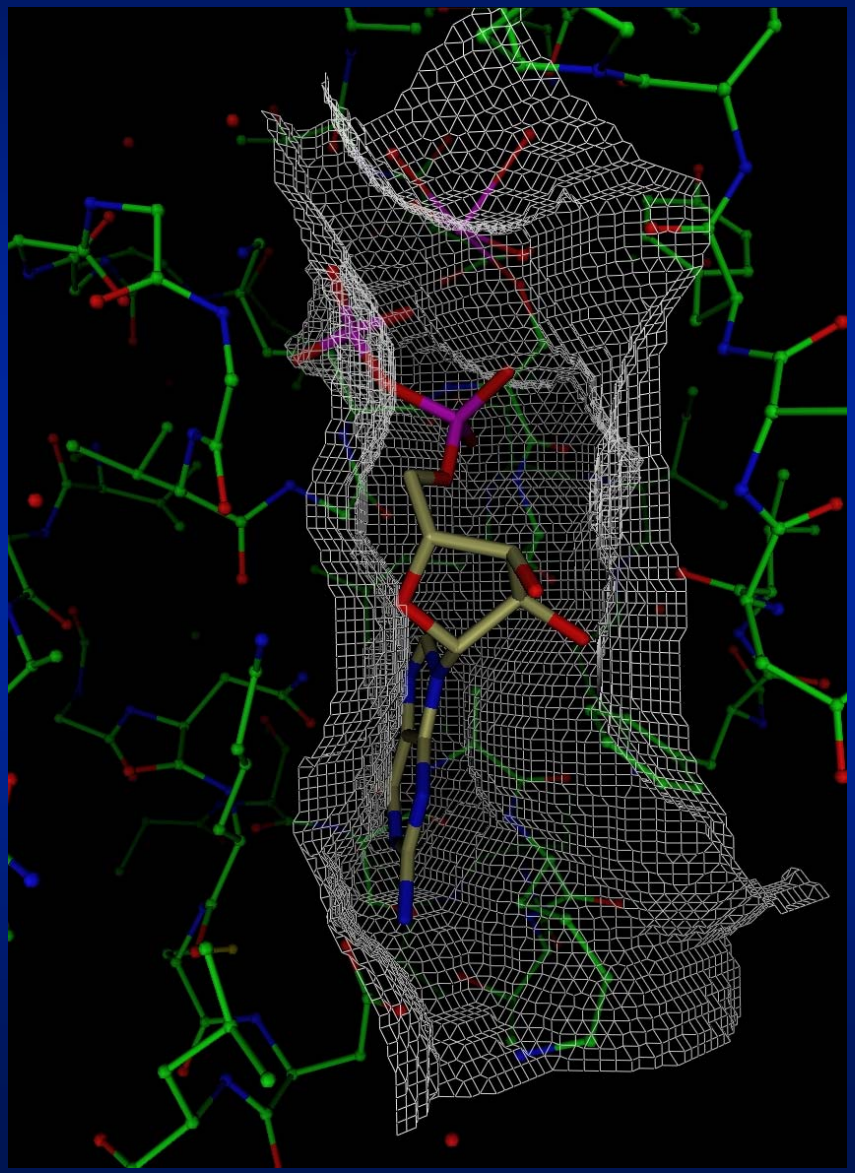


HOPO

Computer–Aided Host Design



Structure-Based Drug Design



Known host structure

- steric constraints
- H-bond regions
- hydrophobic regions

Step 1: Build candidate guests

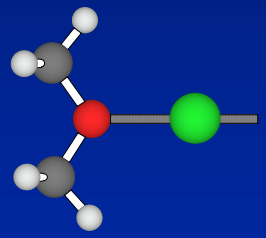
- position functional groups
- link with spacer fragments

Step 2: Score the candidates

- number of H-bonds
- hydrophobic contact area
- entropic factors
- conformational strain energy

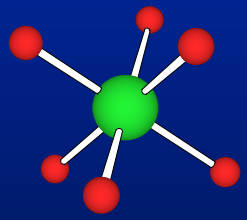
Structure-based host design?

ether binding sites

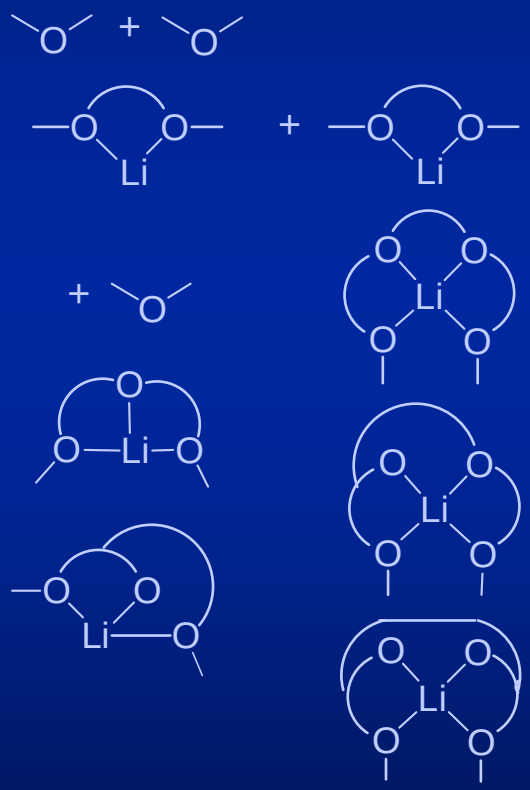


Li–O distance – 2.1 Å

6-coordinate Li^+ complex



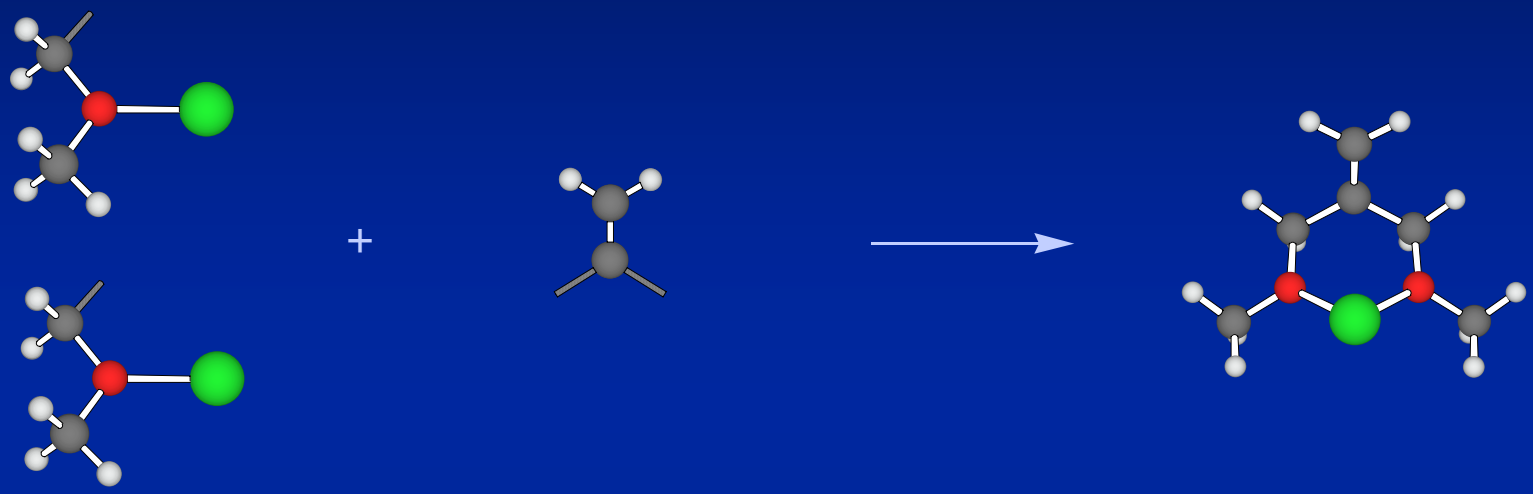
Step 1: building



Step 2: scoring

- geometry evaluation
- strain analysis
- conformational analysis
- QM analysis

HostDesigner Software



Objectives:

Build structures by connecting host fragments with linking fragments

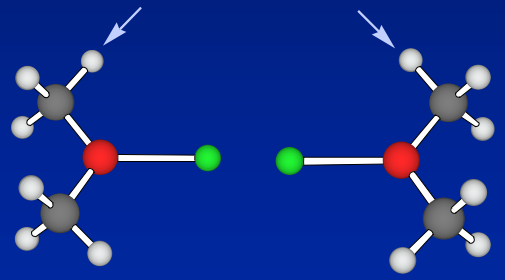
- examine all possible connectivities
- examine all conformations for each connectivity

Score structures with respect to how well they complement the guest.

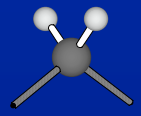
Do it quickly.

Building algorithm - combine three fragments

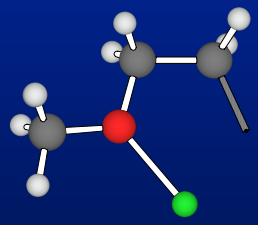
(1) Define two host fragments



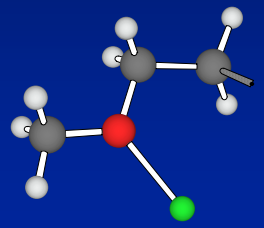
(2) Choose a potential link



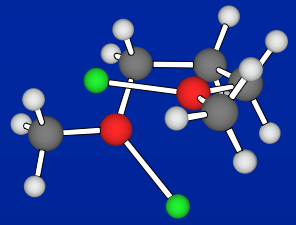
(3) Bond 1st fragment to link



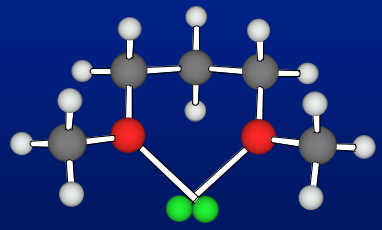
(4) Set dihedral angle on bond



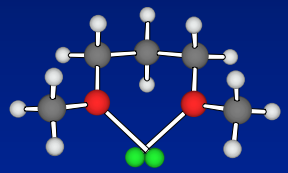
(5) Bond 2nd fragment to link



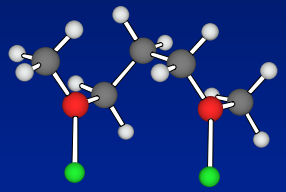
(6) Set dihedral angle on bond



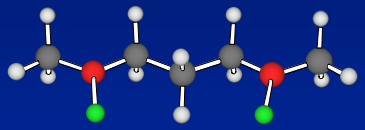
Scoring by geometry



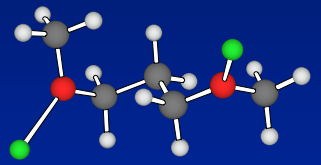
0.50 Å



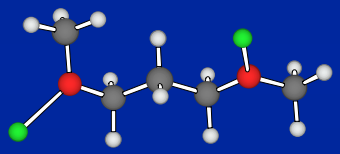
3.42 Å



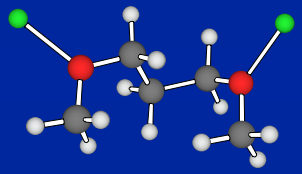
4.50 Å



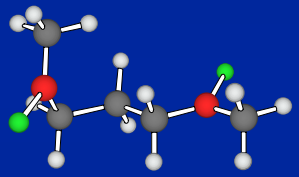
6.35 Å



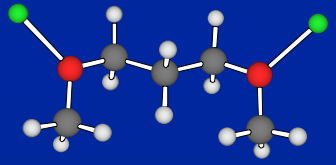
6.59 Å



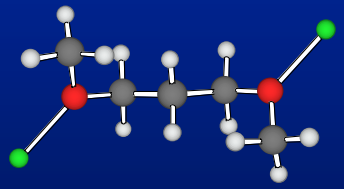
6.84 Å



6.89 Å



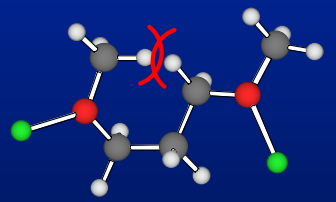
7.64 Å



8.20 Å

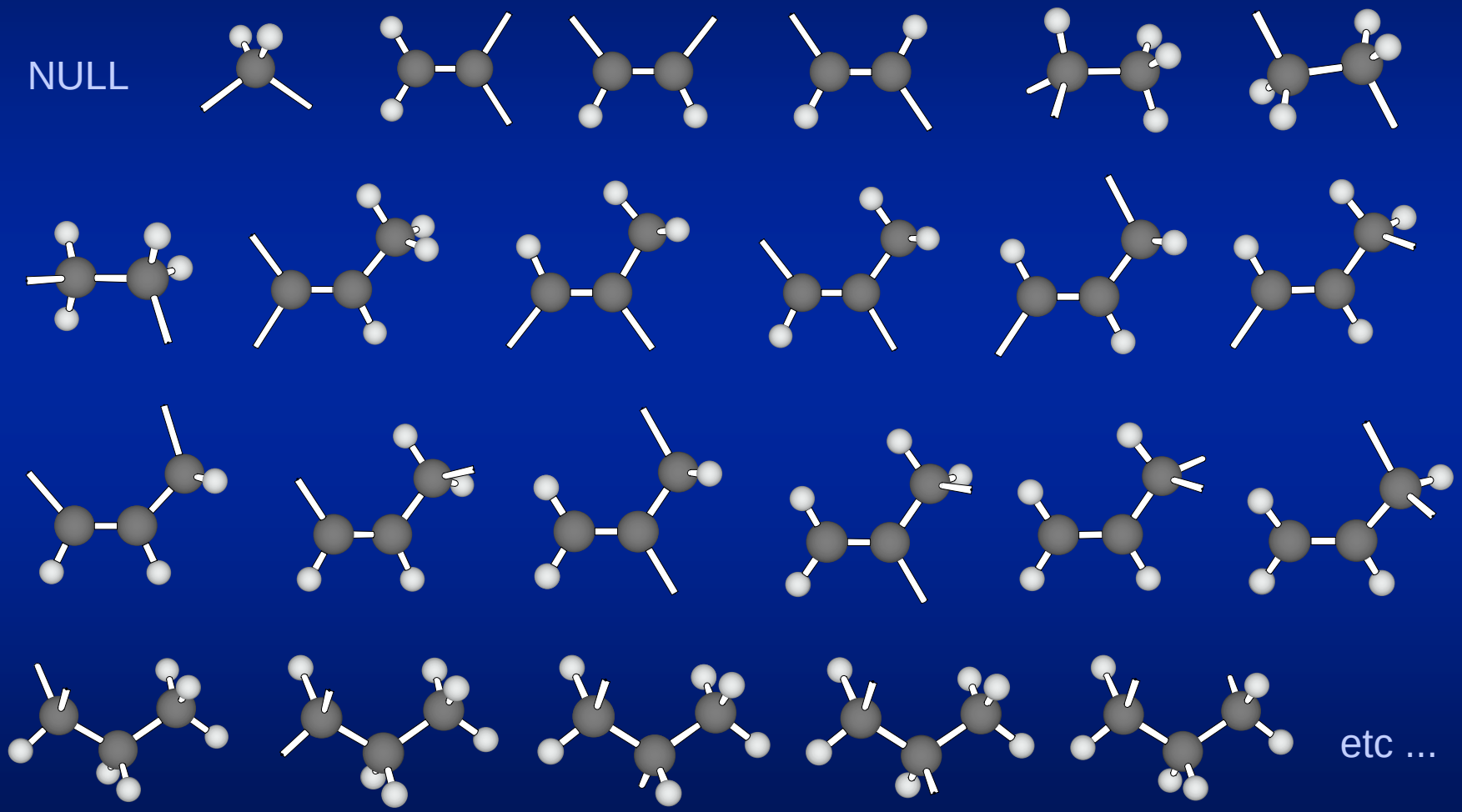
generates 81 structures from methylene linkage

finds only 9 unique structures

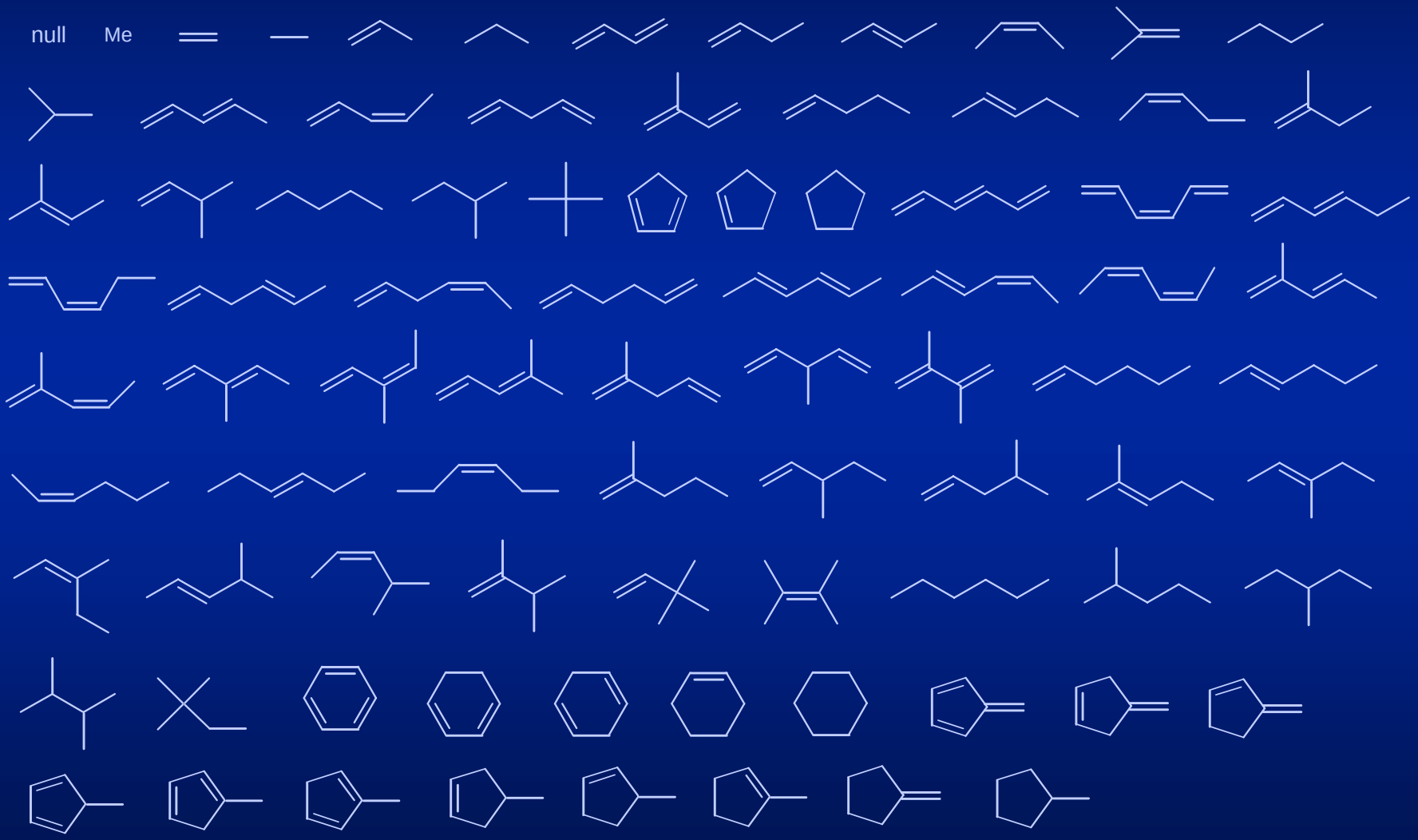


rejected

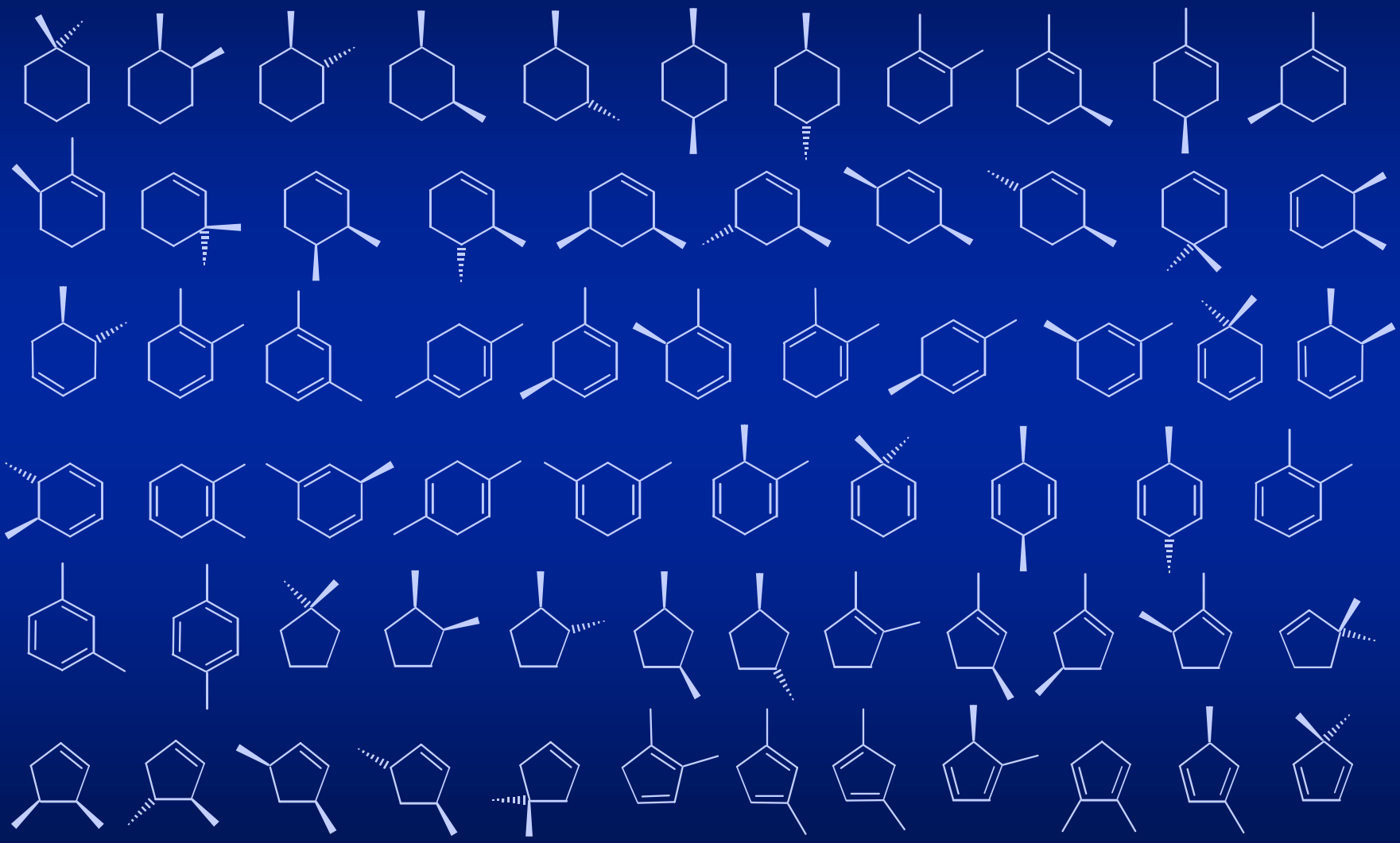
Linking fragment database



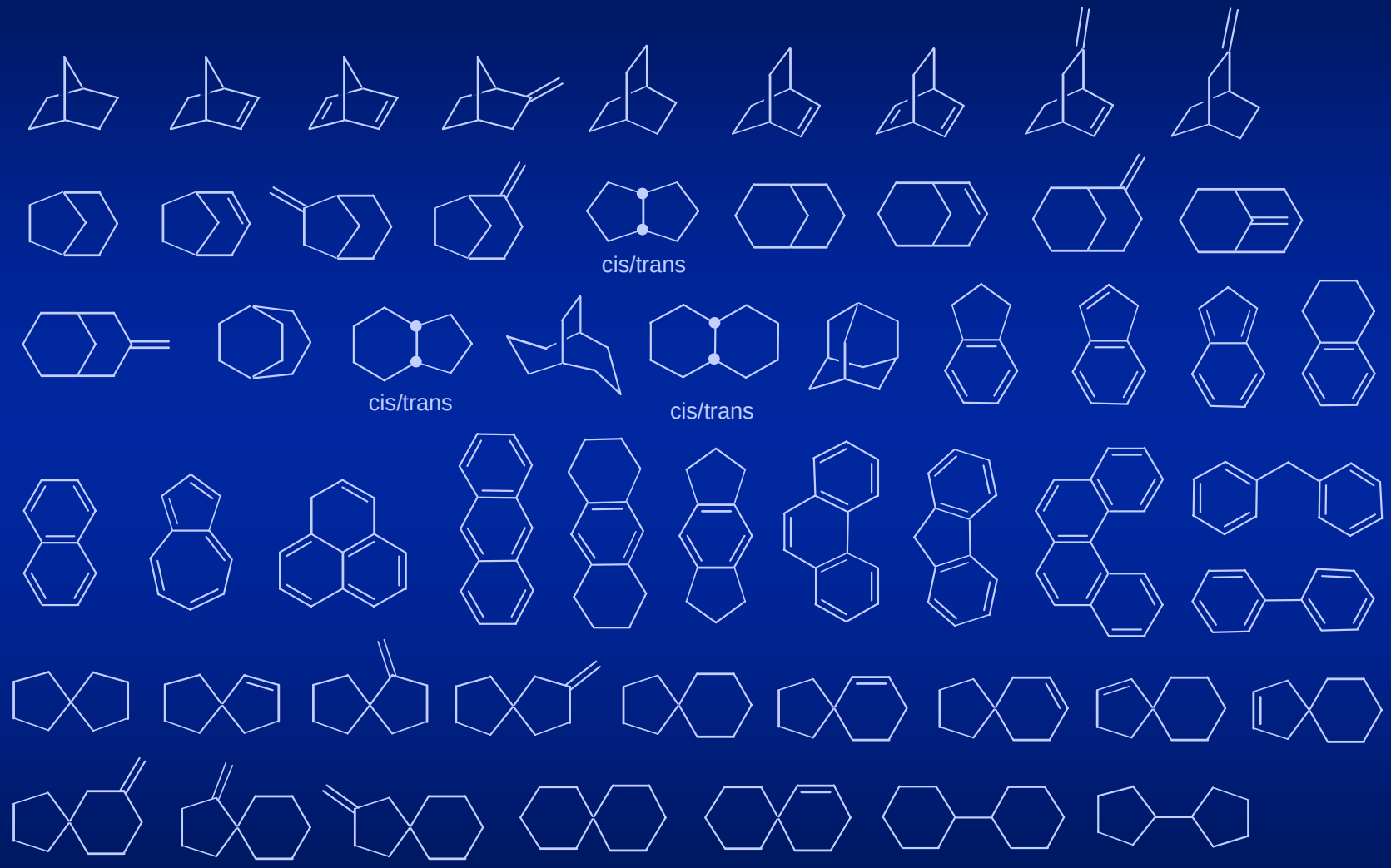
C_nH_m for n = 0 - 6 (excluding alkynes, 3-membered rings, and 4-membered rings)



Dimethylated 5– and 6–membered rings



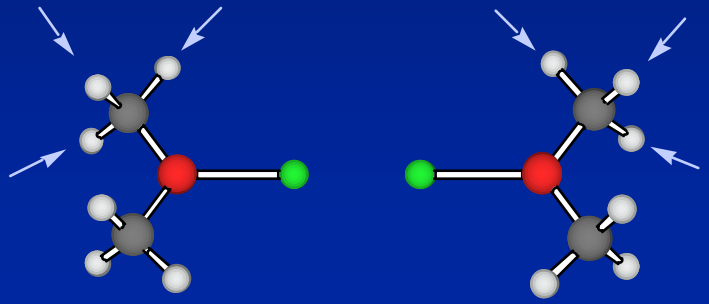
Selected fused–rings



total: 11,297 linking structures

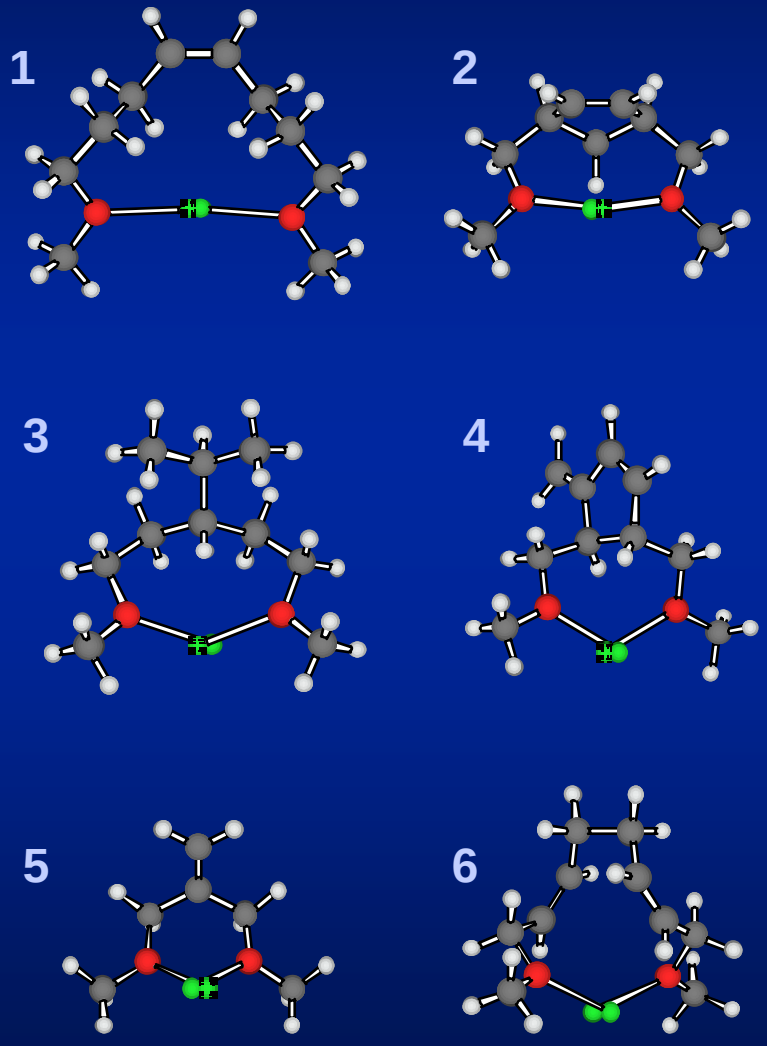
Example run

Input:



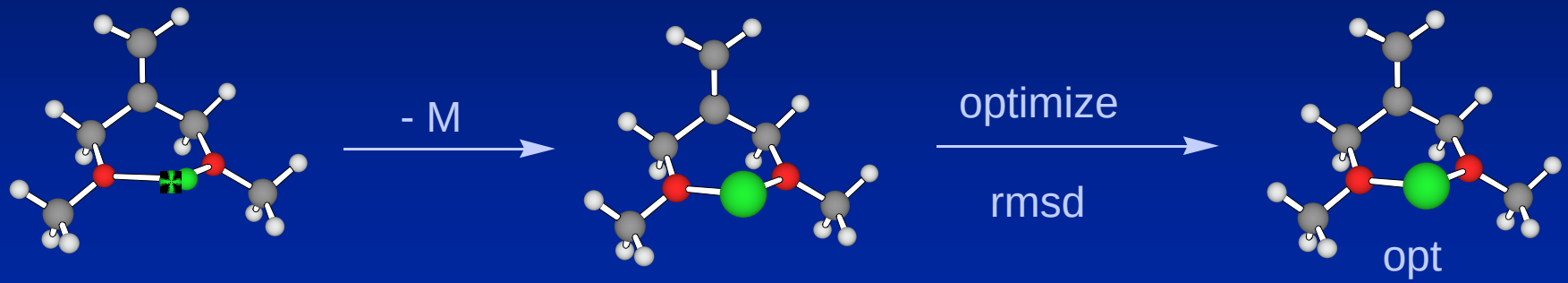
Output: 2,093,217 host structures in 20 sec (MacOSX, 2 GHz)

105,000 structures/sec ! ! !



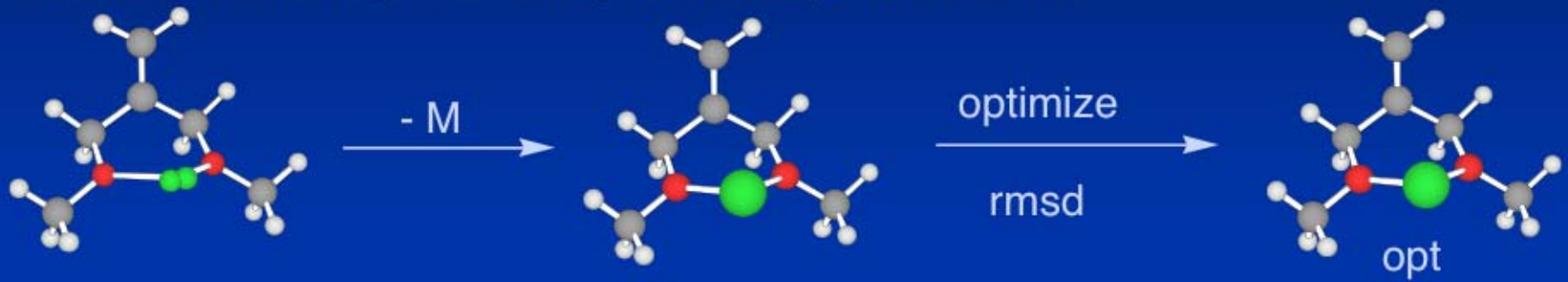
Validation

Are the structures generated by HostDesigner accurate?



Validation

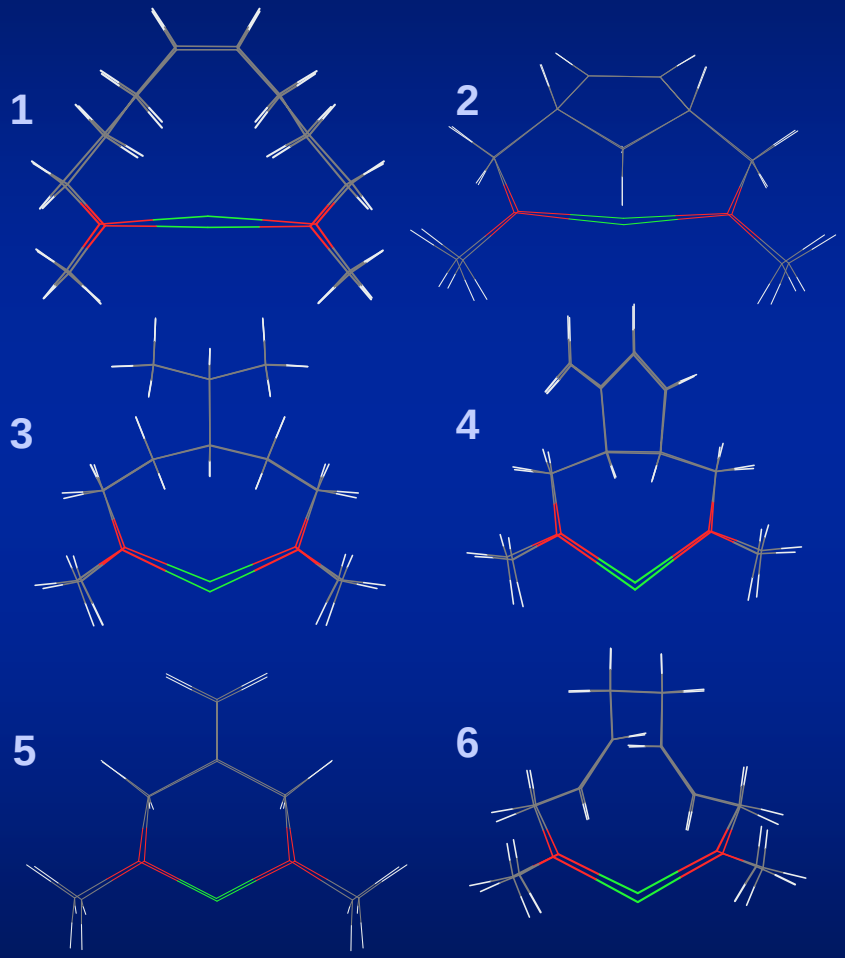
Are the structures generated by HostDesigner accurate?



Do the structures complement the guest?

How did we do?

Are the structures minima?



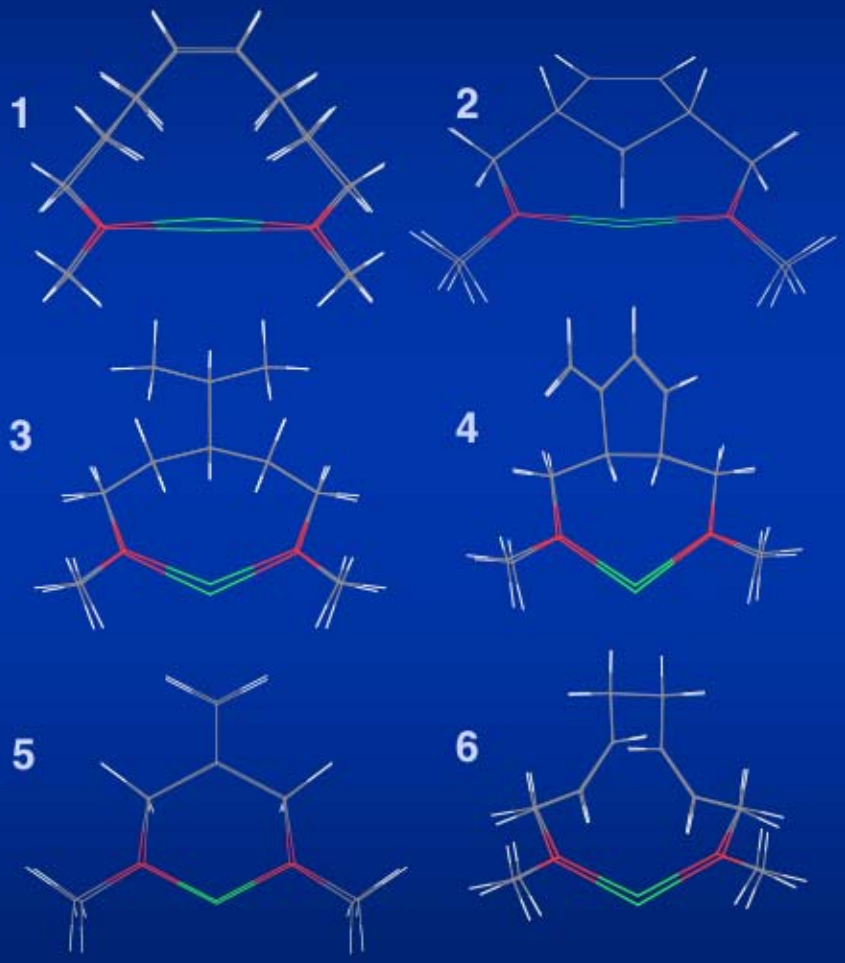
host	rmsd (Å)
1	0.12
2	0.11
3	0.09
4	0.08
5	0.10
6	0.11

Hay, B. P.; Firman, T. J. *Inorg. Chem.* **2002**, *41*, 5502

How did we do?

Are the structures minima?

Are the structures complementary?

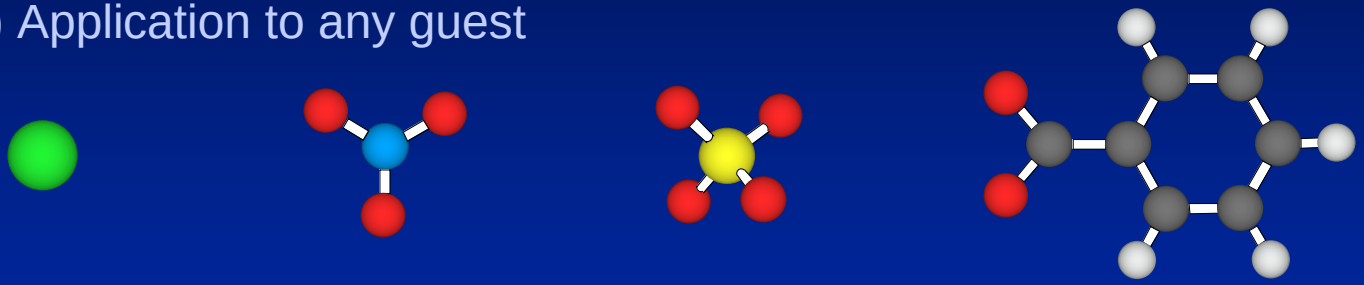


host	rmsd (Å)	ΔU (kcal/mol)
1	0.12	0.23
2	0.11	0.21
3	0.09	0.10
4	0.08	0.10
5	0.10	0.08
6	0.11	0.14

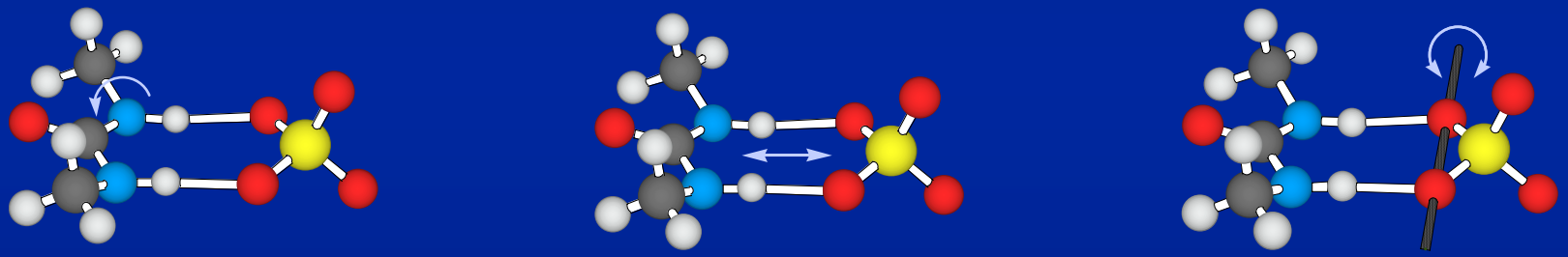
Hay, B. P.; Firman, T. J. *Inorg. Chem.* **2002**, *41*, 5502

Improvements to HostDesigner

(1) Application to any guest



(2) Drive input geometries



(3) Screen out undesirable linkages (chiral, prochiral, linkage isomers)

(4) Estimate conformational energy using a group additivity approach

(5) Optimize code to increase speed

Automated three-stage scoring process

millions of structures

ranked by geometry and estimated degree of preorganization — minutes

top 5000 hits

molecular mechanics analysis ranked by strain energy (ΔU_2) — hours

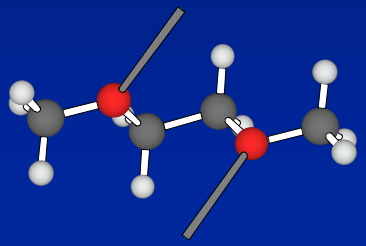
top 500 hits

conformational analysis of hosts ranked by total strain energy ($\Delta U_1 + \Delta U_2$) — days

best hits

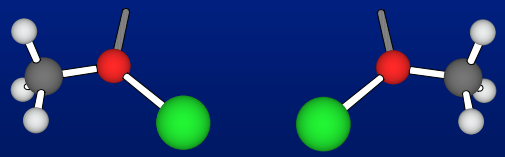
First application to design of metal receptors

Crown ether building block poorly organized for metal ion binding



Organized building blocks should yield more effective macrocycles

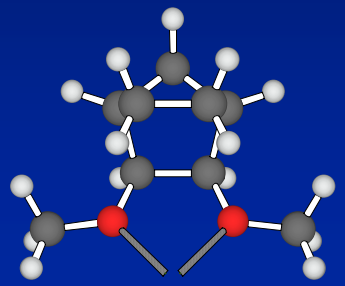
fragment library

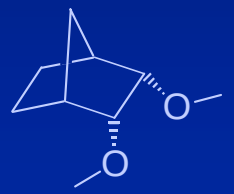


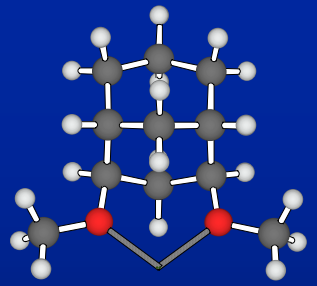
build

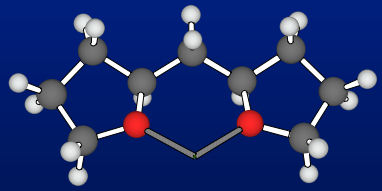
score

Some of the top hits:







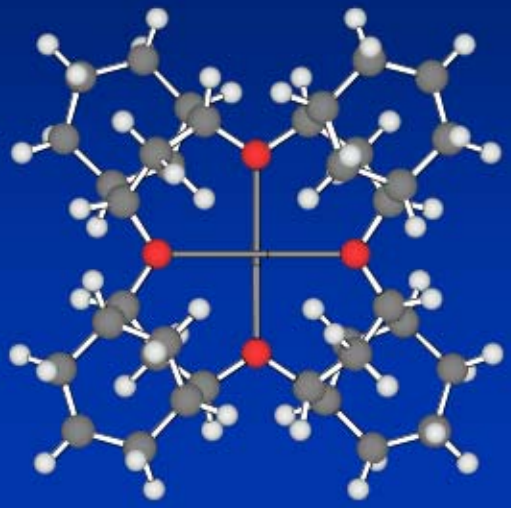


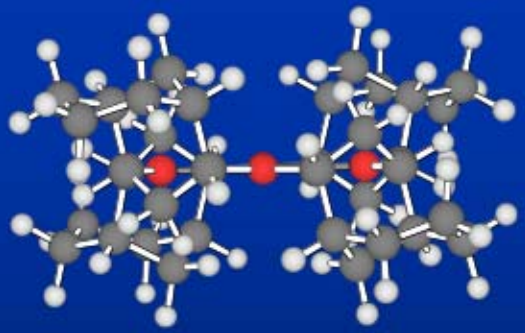
Conventional crown

RHF/6-31G* binding energies

ΔE_{Na}= –91.1 kcal/mol

Designer crown



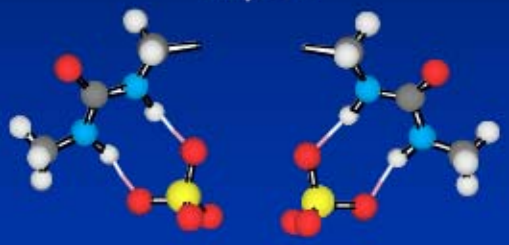


ΔE_{Na} = –94.5 kcal/mol

Hay, B. P.; Oliferenko, A. A.; Uddin, J.; Zhang, C.; Firman, T. K. *J. Am. Chem. Soc.* **2005**, *127*, 17043.

First application to the design of anionophores

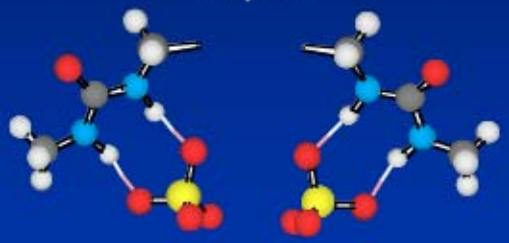
Input



- no linkage isomers
- drive N–C rotation, ± 90°
- drive H - - O distance, ± 0.1 Å
- drive O - - O rotation, ± 30°

First application to the design of anionophores

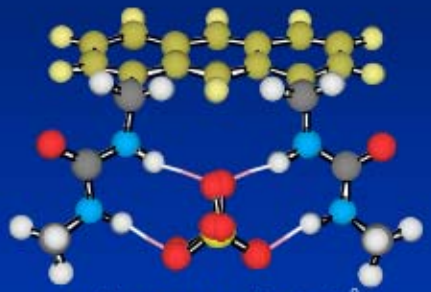
Input



- no linkage isomers
- drive N–C rotation, ± 90°
- drive H - - O distance, ± 0.1 Å
- drive O - - O rotation, ± 30°

587,953,173 configurations
examined in ~10 hr
(MacOSX, 2 GHz)

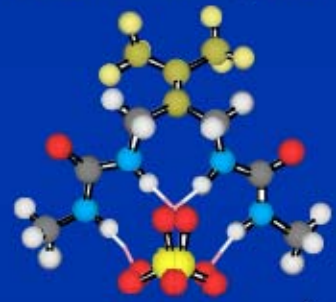
Output



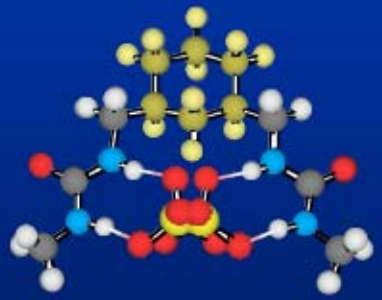
anthracene (0.21 Å)

1,2-*cis*-ethene (0.23 Å)

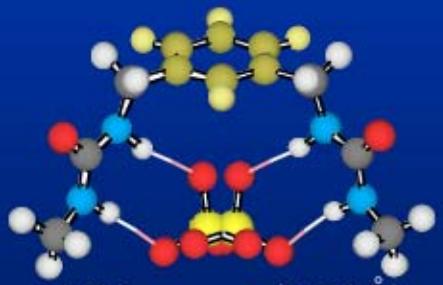
1,2-*trans*-alkene (0.32 Å)



1,1-alkene (0.45 Å)



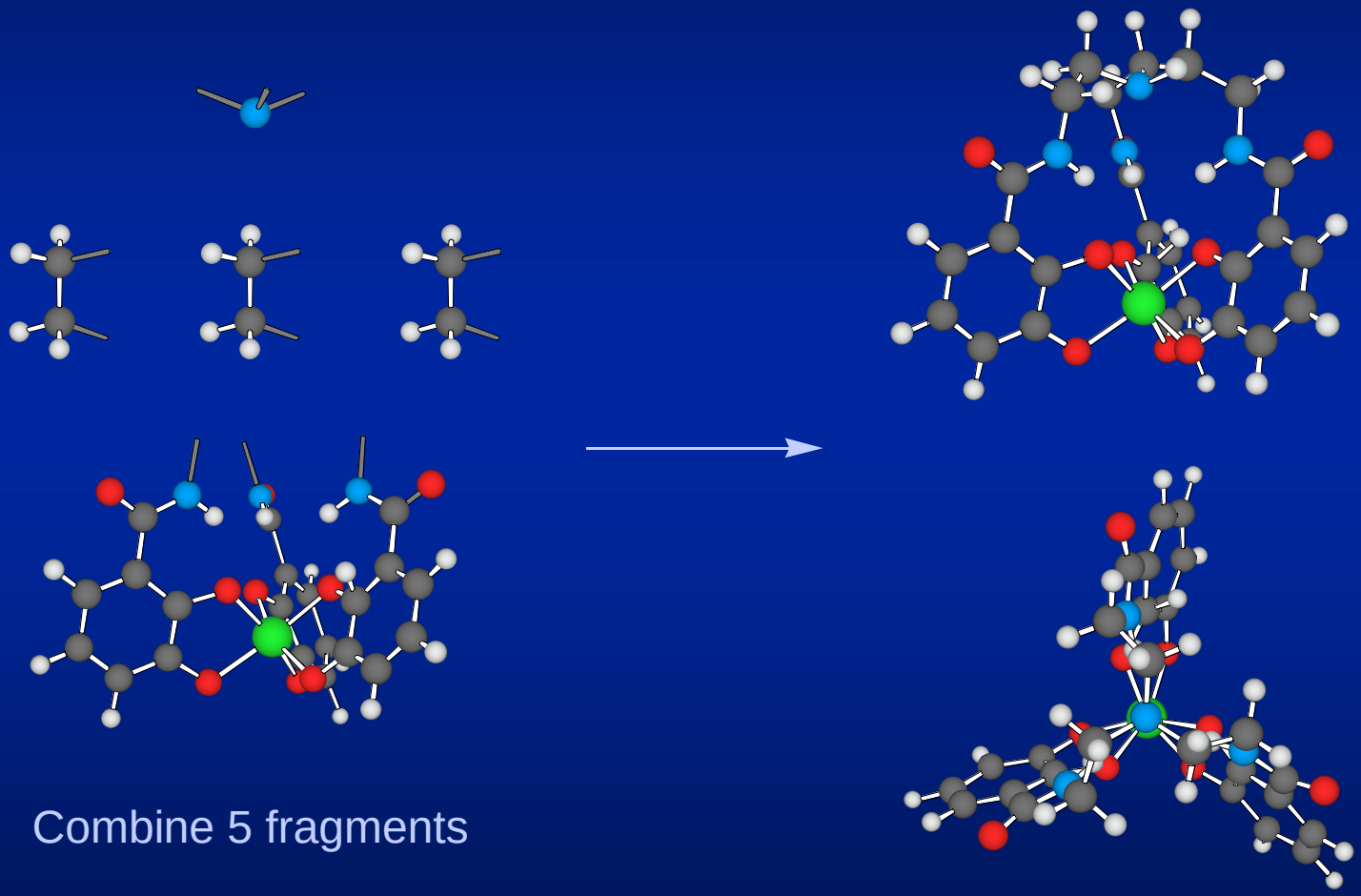
1,3-*cis*-cyclohexane (0.78 Å)



1,3-benzene (0.84 Å)

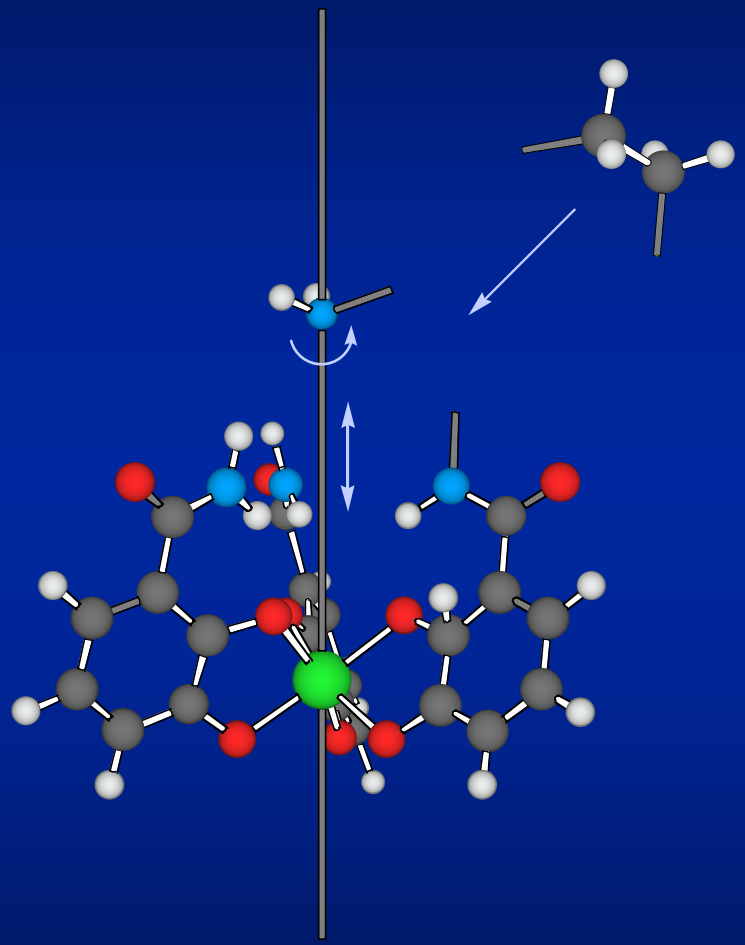
Bryantsev, V. S.; Hay, B. P. *J. Am. Chem. Soc.* **2006**, *128*, 2035.

Assembling larger host molecules - in progress



Combine 5 fragments

Approach



C_3 axis

(1) Input fragment must have symmetry

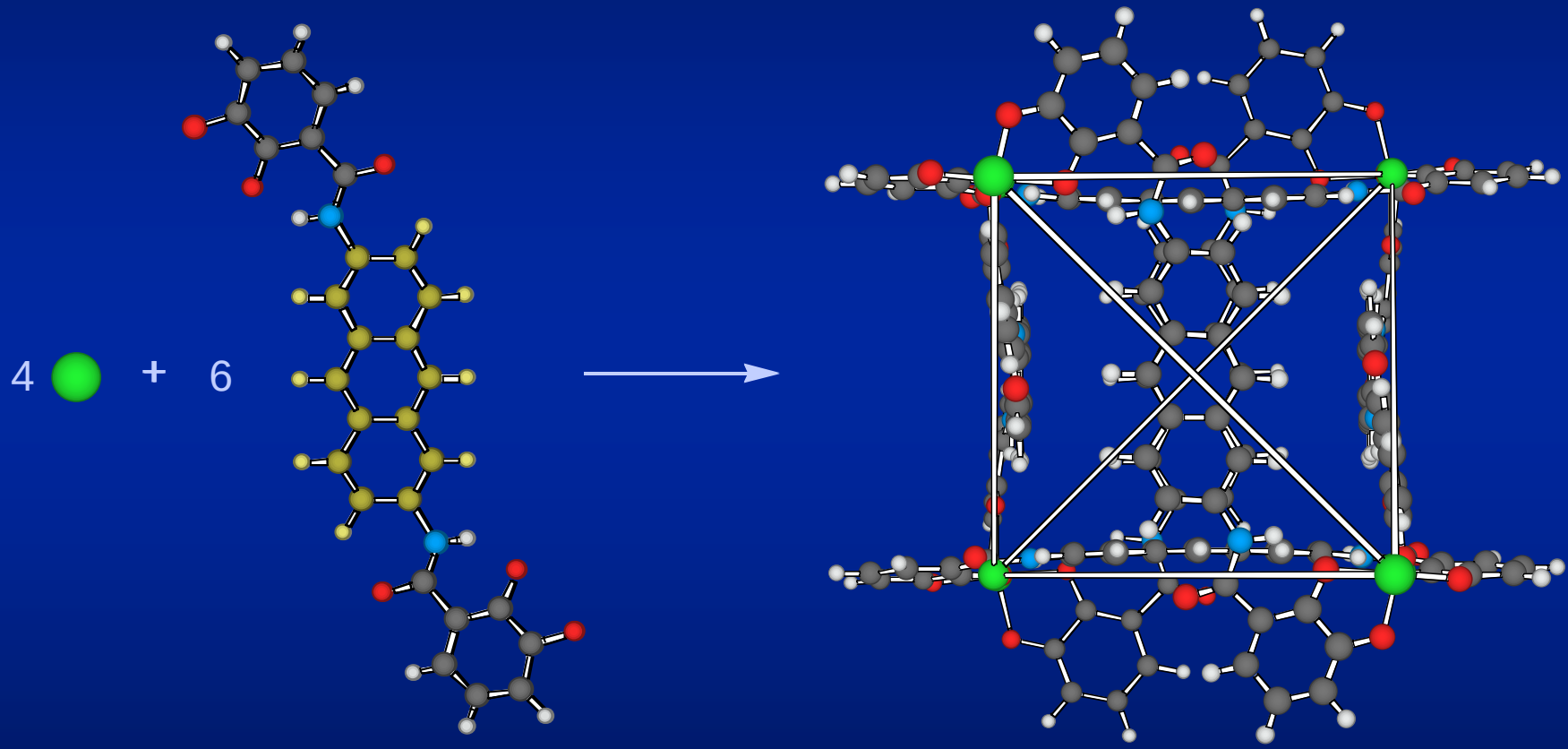
(2) Move and rotate amine on C_3 axis

(3) Find link that overlays bond vectors

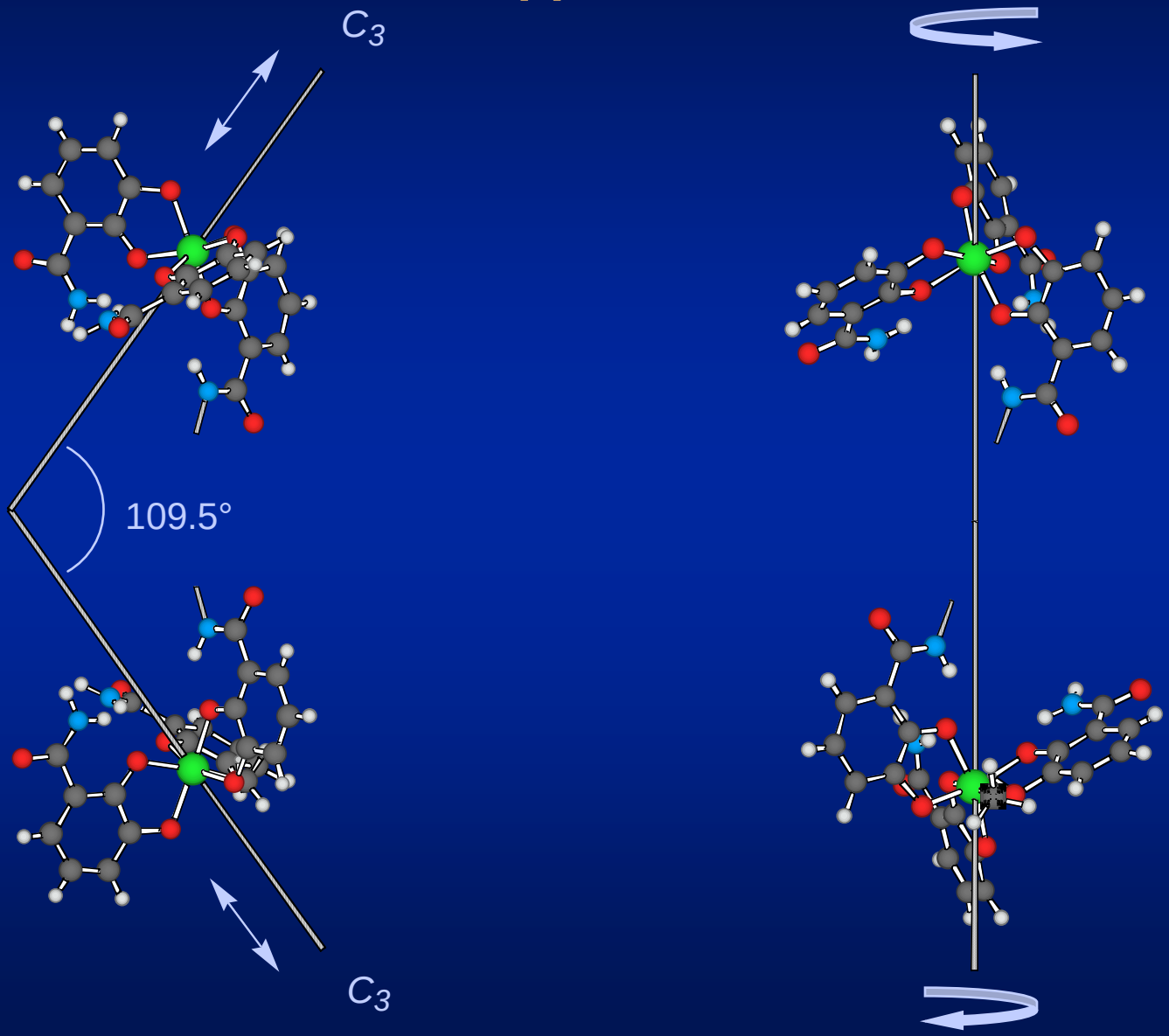
(4) Add links to symmetric attachment points

(5) Check for inter-link collisions

Designing supramolecular assemblies - in progress

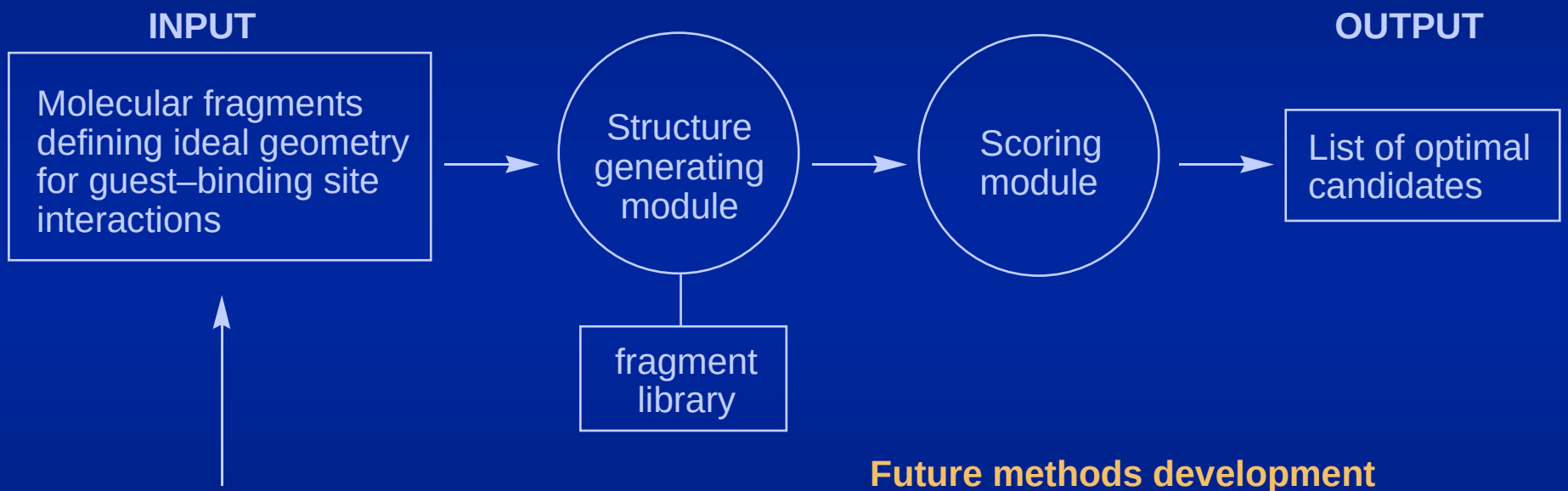


Approach



Summary

A structure-based molecular design approach for the discovery of ion receptors has been developed and automated

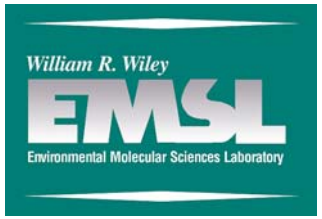


Fundamental studies

- molecular structure
- potential energy surfaces
- nature of bonding interactions
- structure-function relationships

Future methods development

- new molecule building algorithms
- extending the fragment library
- force field parameterization
- improved scoring methods
- faster conformational analysis algorithms



Structure-function research, scoring methods, and applications

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